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Optimization of electrical stimulation parameters for electro-responsive hydrogels for biomedical applications

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ABSTRACT: Electro-responsive hydrogels (ERH) are highly researched materials for biomedical applications. However, most of the research is concentrated on the synthesis of novel hydrogels for various applications, and little effort has been made to investigate electrode configuration and optimization of electrical stimulation parameters. This article used a three-dimensional interdigitated (IDT) electrode configuration device to investigate the optimization of electrical actuation parameters in order to radially deswell an ERH. A Pluronic-bismethacrylate hydrogel modified with hydrolyzed methacrylic acid was used as the ERH material. This article reports on using novel electro-actuation parameters and electrode configurations to maximize radial deswelling of an ERH for biomedical applications. The optimal waveform was assessed for, varying electrode spacing's, voltages, duty cycles, and frequencies. The results show that a maximum deswelling occurred with a DC pulsed monophasic waveform, with IDT electrodes spaced close enough to create a relatively uniform electric field, with a peak voltage of 5 V at 1 kHz, and 50% duty cycle. This resulted in a deswelling of 320% in Krebs solution. Electrochemical impedance spectroscopy results show that the impedance is dependent on the ionic concentration of the fluid environment and that the impedance decreases with increasing frequency. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 41687.

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INTRODUCTION

Hydrogels have a unique ability to absorb water, which allows them to swell up to several thousand times their original volume. This feature makes hydrogels an interesting material for medical applications. Stimuli responsive hydrogels are a specialized group of hydrogels that actuate or respond to an external stimulus. These specialized materials have been researched extensively over the past two decades.[1] Stimuli-responsive hydrogels can be designed to react to various external stimuli including: thermal, magnetic, light, or pH.[2–4] However, an electrical stimuli responsive hydrogel is the most common type, because they are the easiest to synthesize and implement into an application.[5]

The most common applications for electro-responsive hydrogels (ERH) include artificial muscles[6] and drug delivery,[7] however applications involving occluding blood vessels have also been reported.[8,9] The ERH can be synthesized to either swell or deswell during an applied electrical bias depending on the application requirements. The exact mechanism of action is currently unknown, but several mechanisms have previously been demonstrated including: charge transfer, pH change, ion concentration, electric field, and pressure change.[10] All of these mechanisms have been shown to stimulate the material by swelling or deswelling the ERH. Most of the research to date has been focused on developing the ERH material, and future research will be dedicated to implementing the material into an application. One area which has not been reported on and which will be required in order to use the ERH in an application specific situation is the optimization of the external stimulus. Currently researchers are interested in synthesizing the materials for a specific application and performing benchtop testing. Electrical stimulation parameters for benchtop testing are not critical. However, the parameters are critical for *in vivo* applications, because a high electrical current can damage tissue or have fatal consequences.[11]

Researchers typically use flat sheet electrodes using a DC electric field in order to determine the electro-responsiveness of the ERH.[12] The sheet electrodes cause the ERH to bend. A slow pulsed DC electric field with a low frequency of 0.4 MHz (a pulse every 40 minutes) was previously used to demonstrate that an ERH could respond to a switching electric field.[13] Previously the authors demonstrated that an interdigitated (IDT) electrode configuration could be used to generate a uniform electric field around a cylindrical ERH, which causes radial swelling/deswelling of the hydrogel rather than bending,[8] which is desired for some applications like occluding a blood vessel. A DC electrical bias is acceptable to use during external actuation, however for *in vivo* applications DC biasing can cause tissue damage, and it is likely to generate electrolysis and pH changes because the high current levels required to actuate the ERH are typically several mA up to hundreds of mA. The goal of this article is to investigate optimal stimulation parameters that will increase the deswelling capabilities of ERH while reducing the risks involved in *in vivo* electrical stimulation. This article reports on the optimal bias parameters for one particular ERH, but the key factors should be similar for other ERH. Deswelling is important for most implantable applications as the hydrogel should be small while being implanted. For example in a blood vessel occlusion application the hydrogel has to be small enough to be transported through the blood vessels, and then swell at the target location.

This article investigates the electrical bias parameters required to deswell a synthesized Pluronic/methacrylic acid sodium salt hydrogel using an IDT electrode configuration. The modified Pluronic material has been previously demonstrated to be electro-responsive.[14] Currently, there have not been any reports on the optimization of the electrical bias parameters required to cause swelling/deswelling of ERH. This article investigates a frequency dependent stimulation method for deswelling ERH while increasing the safety of the stimulation for *in vivo* implantable applications. Electrical bias parameters such as frequency, duty cycle, voltage amplitude, electrode configuration, and waveform shape will be investigated within this article. In addition electrochemical impedance spectroscopy (EIS) will be performed on the ERH in order to better determine the effects of varying the electrical bias frequencies. The electrical bias parameters in this article were investigated for the purpose of using the ERH in an implantable biomedical application. Details of the experimental design and results are given below.

EXPERIMENTAL

Synthesis of ERH

The ERH used in this study was a Pluronic/methacrylic acid sodium salt hydrogel (PLMANa). Pluronic F127, is an ABA block copolymer, which was chosen as the base material for the ERH due to its wide use as a biocompatible hydrogel. The modified Pluronics ERH was prepared by crosslinking methacrylate endcapped Pluronic (PF127-BMA) with the sodium salt of methacrylic acid as previously described.[14] Briefly, 1.5 g of PF127-BMA was mixed with 2.4 g of hydrolyzed methacrylic acid and 4.6 g of deionized (DI) water. The DI water was flushed with N_2 gas prior to mixing. An initiator of (0.75 mL) of 1*M* ammonium persulfate (APS) solution was made using DI water flushed with N_2 and APS (Sigma Aldrich A3678). A 1*M* tetramethylethylenediamine (TEMED) (Sigma Aldrich T9281) solution (0.75 mL) was also added to the solution as the accelerator. The solution was slowly mixed and covered with a blanket of N_2 gas in order to avoid oxygen trapping. The solution was then poured into a cylindrical glass mold and refrigerated for 1 hour before transferring the mold to a water bath at 37°C for 3 hours. The mold used in this case was a cylindrical glass container (diameter 20 mm) with cap to prevent oxygen trapping. The thicknesses of the samples were determined from the amount of solution poured into the molds (2 mm).

After polymerization of the ERH the samples were removed from the molds and cut into a cylindrical shapes using a metal biopsy puncher (Miltex instruments) with a diameter of 3 mm. After the samples were punched they were purified in Krebs solution for 3 days. Krebs solution was used for purification because it has similar ionic concentration as blood.[8] Purification was performed to remove any residual material that did not polymerize, which would be required for biocompatibility. The Krebs solution was changed two to three times per day during the 72 hours of purification. Testing of the samples was performed after purification. The samples were allowed to passively swell in the Krebs solution during purification. Swelling (S) was determined by weighing the dried samples (W_d) and the swollen samples (W_s) using the following formula:

$$S=\frac{W_S-W_d}{W_d}\times 100\% \tag{1}$$

Three-Dimensional (3D) IDT Electrode Device

The ability of the PLMANa hydrogel to respond to an electrical bias was previously reported using sheet electrodes to investigate bending of the ERH.[15] This article aims to investigate optimal stimulation parameters that cause radial deswelling of the ERH. In order to accomplish this, a 3D macro-scale IDT electrode configuration device was developed. Previously, a 3D IDT electrode configuration demonstrated radial deswelling of a cylindrical ERH.[8] The IDT electrode configuration has been previously shown to create a relatively uniform electric field around the ERH.

The 3D IDT electrode consisted of a Perspex device with holes drilled through the base, with 500 μm diameter platinum (Pt) wire extending through the holes to act as the electrodes. The Pt wire was chosen for the electrodes as Pt does not dissolve under an electrical bias in a chloride-rich electrolyte. A center hole in the Perspex allows the hydrogel to be held in place by low level vacuum. Figure 1 shows a picture of the 3D IDT electrode device and hydrogel sample. Holes were placed every 15° so that different spacing of the electrodes could be tested. The IDT electrodes allow for alternating the cathode and anode biasing so that a uniform electric field can be generated. The diameter of the IDT electrode device allows hydrogels up to 8 mm to be tested.

Electrochemical Impedance Analysis

EIS was used to measure the impedance values of the ERH as a function of frequency. EIS measurements were used to determine the impedance of the hydrogel and how the impedance changes with varying frequency, which can be used to determine how the hydrogel will respond to a frequency dependent electrical bias. For the experiments an electrochemical workstation (CHI 660A, CH Instruments, Tx) was used. The samples were prepared as stated above. Hydrogel samples with different swelling properties, due to the swelling media ion concentration, were tested ($n = 4$ each). The impedance measurements were also used to determine the relaxation time for the ERH and to

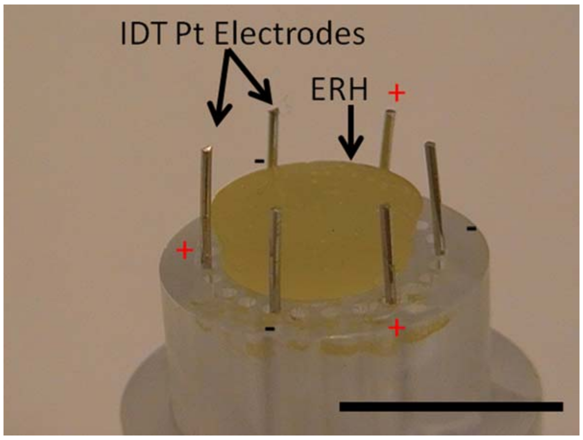

Figure 1. Picture of the IDT electrode test setup with ERH in the middle between Platinum wires with alternating cathode and anode electrodes. Scale bar is 1 cm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

determine the impedance values for the hydrogel as a function of frequency and various swelling rates. The measured samples were swollen in Krebs, DI water, and unswollen (directly after polymerization). A 3-electrode configuration was used to make the measurements.[16–18] A Pt wire was used as the counter electrode, and a Ag/AgCl wire was used as the reference electrode, both of which were placed in a phosphate buffer solution (PBS). The working electrode consisted of a Pt wire that was manually inserted into the center of the ERH in order to connect with the EIS machine, and the hydrogel was placed in the PBS solution. The working electrode was insulated with a nonconducting epoxy except for the tip. An AC voltage of 15 mV rms sine wave (voltage verified to be in linear range of the hydrogel) was applied between the reference and working electrode, while current was measured between the counter and working electrodes. A frequency sweep between 1 Hz and 100 kHz was performed on each sample. After the measurements were performed the results were analyzed by fitting the results to an equivalent electrical circuit model using ZSimpWin (Princeton Applied Research) software. Equivalent circuit modeling (ECM) is the most common method used to analyze EIS data. ECM describes the behavior of each element in terms of classical or specialized electrical components, so that they can be further analyzed.

Optimization of Electrical Bias Parameters

The electrical bias testing was performed after purification when the samples were swollen in Krebs solution. The electrical bias was performed in a 3*M* KCl solution, so deswelling of the ERH will occur due to a significant difference in ionic concentration. The 3*M* KCl was used as the biasing solution because it has a higher ionic concentration than the solution used to purify the samples, but if the ERH were purified in DI water, Krebs solution could be used for the biasing solution.[9] Hydrogel control samples were used without an applied electrical bias. All the electrical biasing tests consisted of applying a bias for 1 hour; the samples were weighed every 15 minutes in order to measure their swelling/deswelling. After 1 hour the samples were placed back into Krebs solution to passively swell. This type of test setup was used to mimic an application where an electrical bias is used to deswell the ERH and then the material is allowed to re-swell in the body. Krebs solution was used as the material to passively swell the ERH because it has the same ionic concentration as blood, and hydrogels have been demonstrated to respond the same in Krebs as in blood plasma.[14]

Optimal Waveform. Three different waveforms were experimented with to determine the optimal waveform shape to deswell the hydrogel. A DC bias is the most common waveform used for electrical biasing of ERH. However, DC biasing at the high voltage and current levels needed to deswell the hydrogel in this application are not safe to use *in vivo*. The high electrical bias parameters would cause an irreversible faradaic reaction through electrolysis, which could cause damage to the tissue when implanted.[19,20] Results of a DC bias experiment were previously reported.[8] Three different waveforms which are less likely to cause irreversible faradaic reactions were investigated in this article including: monophasic, biphasic, and AC sinusoidal as shown in Figure 2.

The ERH samples were prepared using the methods stated earlier and tested using the 3D IDT electrodes and test setup described above. The ERH samples ($n = 5$ each) deswelling values were measured using eq. (1). The electrical bias parameters used consisted of $V_{PP} = 5$ V with a frequency of 1 kHz and a Duty cycle of 50%. The samples were deswelled under an electrical bias for 1 hour and then the bias was removed to allow the ERH to passively swell.

Optimal Electrode Spacing. The concept of the 3D IDT electrode configuration was to create a relatively uniform electric field around the perimeter of the hydrogel, thus deswelling the ERH radially so that it can be transported through the body via a blood vessel. Previous finite element modeling analysis showed that uniformity of the electric field was dependent on the spacing of the IDT electrodes.[8] Three different electrode spacing configurations were tested: 45° (2 mm), 60° (3.5 mm), and 90° (5 mm) with $n = 5$ samples for each configuration. Control samples were used which consisted of un-biased hydrogels. The electrical bias parameters for all of the electrode configurations included a monophasic waveform operating at 1 kHz, 50% duty cycle and 5 V_{PP}. The samples and testing configurations were the same as described earlier.

Optimal Voltage Amplitude. The peak voltage of the electrical bias is known to affect the amount of deswelling in ERH. In order to determine the optimal voltage amplitude four different peak voltages were tested. The 3D IDT electrode configuration was set at 45° (2 mm) separation between electrodes and the waveform was monophasic with a 50% duty cycle operating at

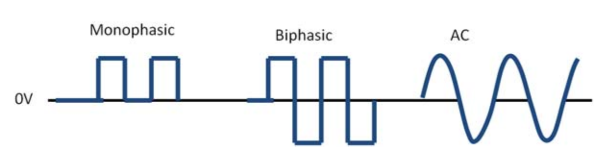

Figure 2. Schematic of different waveforms with 50% duty cycle. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

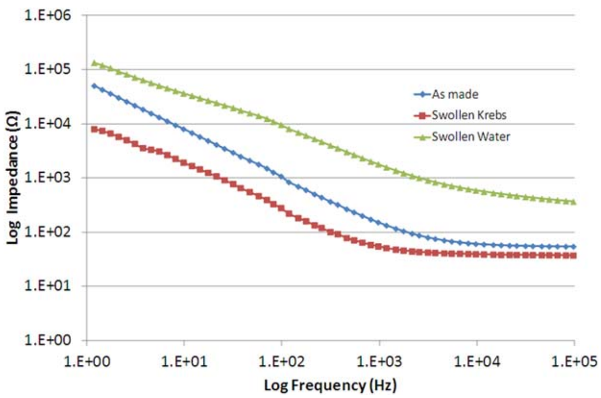

Figure 3. Impedance versus frequency average of three different swelling stages of ERH: as made, after swollen in water, and after swollen in Krebs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

1 kHz. Peak to peak voltages included 1, 3, 5, and 7 V. A universal pH indicator (Sigma Aldrich, 31282) was used to monitor any pH change due to electrolysis which can be caused from increasing the voltage. $N = 5$ samples of each voltage were tested. The pH needs to be monitored because hydrogels will deswell/swell based on change in pH, so monitoring the pH levels help to ensure that the mechanism of action is caused by the electrical stimulus.

Optimal Duty Cycle. The duty cycle is an important parameter in monophasic waveforms as it represents the percentage of applied voltage. Four different duty cycles were tested with $n = 5$ samples each. The duty cycles included 20%, 40%, 60%, and 80% and control samples with no applied electrical bias. A monophasic waveform with 4 V_{pp}, 1 kHz, and electrode spacing every 45° (2 mm) were kept constant throughout the testing. A universal pH indicator was used to monitor any pH change due to increasing the duty cycle and electrolysis was visually inspected.

Optimal Frequency. As stated earlier, typical stimulation parameters for ERH use a DC electrical bias. However; a DC bias is not a safe option for implantable materials. A monophasic waveform is safer, however; the optimal frequency has to be determined. Typically a higher frequency bias will have an increased threshold for pain and tissue damage.[11] However, the effect on the deswelling of the ERH is unknown. For this experiment a monophasic waveform with electrodes spaced every 45° (2 mm) with a 4 V_{pp}, and 50% duty cycle were used. Four different frequencies were tested with $n = 5$ samples each which included 1 Hz, 100 Hz, 1 kHz, and 10 kHz. A universal pH indicator solution was used as described earlier to monitor any changes in pH and electrolysis was visually inspected.

Optimal Electrical Bias Properties. Once the above experiments were performed and analyzed the various parameters were combined to test the deswelling capabilities using the optimal electrical bias settings. Two sets of optimal values were tested, one which includes the optimal parameters for use in biomedical applications (no pH changes or electrolysis), and one for non-biomedical applications where pH changes and electrolysis are acceptable. Using the results from the above tests a numerical model was developed in order to predict the amount of deswelling and the results were compared with experimental results in order to determine the accuracy of the model.

RESULTS AND DISCUSSION

Passive swelling of the ERH after purification in Krebs solution typically resulted in a 2.5× increase in diameter and an average mass swelling of approximately 450%–500%. The average impedance versus frequency of the ERH samples using the EIS is shown in Figure 3. Figure 3 shows the average results for ERH with three different types of treatments. All three sample types respond similarly to a change in frequency. The results show that the ERH samples that were swelled in Krebs ionic solution have the lowest impedance, which is expected since the ionic solution contains more ions than the DI water, which would make the hydrogel samples more conducting. The samples tested after synthesis have a lower impedance than the samples swollen in DI water. DI water swollen hydrogels were expected to have the highest impedance because the hydrogel has maximum swelling and the lowest quantity of ions. At approximately 1 kHz the impedance flattens in all three sets of samples and the phase (not shown) approaches 0° which means the double layer capacitor becomes open.

In order to further analyze the impedance measurements an electrical circuit model (Figure 4) was developed. Similar electrical circuit models have been used previously to describe the behavior of ERH.[21] The R_s represents the electrolyte resistance, the R_{ct} (charge transfer resistance), and W (Warburg) represent the faradaic impedance of the material, and the Q is the constant phase element which represents the double layer capacitor. Fitting the impedance results for the hydrogels in Krebs solution to the electrical circuit model allowed us to determine relaxation time of the ERH by determining the R and C values of the circuit. The relaxation time of a ERH represents the frequency at which the polyelectrolyte molecules in the hydrogel are not able to respond because the frequency is too fast.[22,23] This means that for a pulsating bias if the frequency is high enough the ERH will not have time to swell during the period where 0 V is applied. Typically, ERH placed under an applied bias in a high ionic concentrated solution will shrink due to diffusion of ions, however when the bias is removed the hydrogel will passively swell due to absorbance of fluid. However, if the frequency is high enough the hydrogel will not have time to

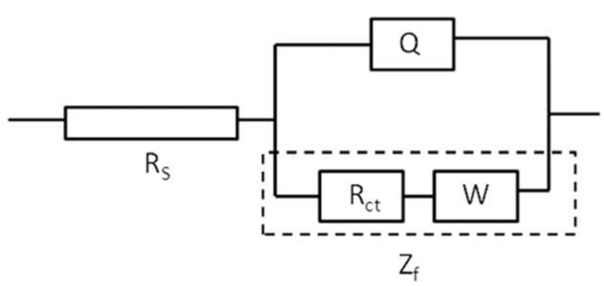

Figure 4. Equivalent circuit model of electro-responsive hydrogel.

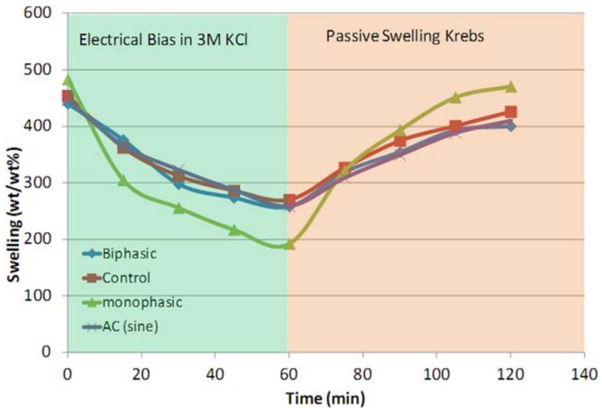

Figure 5. Swelling results for ERH with an applied electrical bias with different shaped waveforms (AC, Biphasic, and Monophasic) with bias properties of 5 V, 1 kHz, and 50% duty cycle. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

respond to the swelling aspect of the waveform, thus allowing the ERH to continuously shrink.

Fitting the experimental results to the electrical circuit model using ZSimpwin software (Princeton Applied Research) gave a relaxation time of 1.074 ms which is equivalent to 931 Hz. Typically under DC biasing ERH samples are always being stimulated. However, for pulsed DC or monophasic biasing there are periods of high and low (0V) voltages being applied as shown in Figure 2. This type of pulsating bias has been demonstrated for drug delivery previously.[7,24] However, in these cases the pulses were long (60 minutes) so the ERH had time to relax, and as expected the hydrogels swell during this period. Several applications such as occluding a blood vessel requires the ERH to continuously deswell, so an electrical bias that is above the relaxation time is ideal in order to prevent the ERH from passively swelling during the low voltage level.

The results for the optimal waveform are shown in Figure 5. During the electrical bias (first 60 minutes) the average AC sine wave and biphasic waveforms had no significant difference in deswelling rate when compared with the control (un-biased samples). Both set of samples had significant deswelling from approximately 450%–275%, but this is similar to the control. The control samples deswell because they are going from low ionic concentrated (Krebs) solution to a high ionic solution (3*M* KCl), so the hydrogels will shrink due to diffusion of ions. The monophasic (pulsed DC square waveform) on the other hand had significantly more deswelling than the control, reducing its volume expansion to 190% of its original mass after 60 minutes of an applied bias. The AC and biphasic waveforms deswelling rate did not differ from the control because the voltages were alternating between positive and negative voltages, with equal duration. Typically ERH swell or deswell near the cathode or anode, so electrodes with switching anode and cathodes, as with the AC and biphasic waveform, the two effects cancel each other out and there is a zero deswelling effect due to the applied voltage. On the other hand the monophasic waveform switches from an applied voltage to 0 V, and since the frequency is above the relaxation frequency the ERH does not have time to respond (swell) during the 0 V stage, so the net effect is a deswelling of the hydrogel due to an applied bias as shown in Figure 5. After 60 minutes the electrical bias was removed and the samples were allowed to passively swell in Krebs solution. Within 1 hour all the samples had swollen back to their original swollen state. During the first 15 minutes the monophasic biased samples had a large increase in swelling which is due to the large difference in ions in the material which were introduced from the applied bias.

Previously it was demonstrated through finite element modeling that the electrode spacing was important to create a relatively uniform electric field around the ERH.[8] The results from the electrode spacing experiment are shown in Figure 6. The results show that the average deswelling for all three electrode spacing configurations were significantly different and that the maximum deswelling increased as the electrodes became closer together. This validates the results from the previous FEM. The ideal electrode configuration would have electrodes that are close together. The 3D IDT electrode device used in this study had a limitation of 45° separation, however closer separation would likely result in an increase in deswelling. The passive swelling results are similar to the results in Figure 5. The hydrogels return to their original swollen state after 1 hour and the most deswelled samples have a larger rate of swelling within the first 15 minutes of being allowed to passively swell.

Figure 7 shows the results from increasing the peak to peak voltage. As expected, as the applied voltage was increased the deswelling rates also increased. The 1 and 3 V samples showed significant difference in deswelling compared with the control samples, but the deswelling rates were much lower than with 5 and 7 V. The 5 and 7 V peak to peak ERH samples showed significantly more deswelling, but the difference between the 5 and 7 V was minimal. The increased deswelling was caused by increasing the electric field which increases the amount of ions diffusing into the ERH. For all of the voltages except 7 V there were no visual signs of electrolysis or pH change due to the high frequency, 50% duty cycle and monophasic stimulation.

Duty Cycle for a pulsed DC waveform is an important parameter because it represents the amount of time that the voltage is

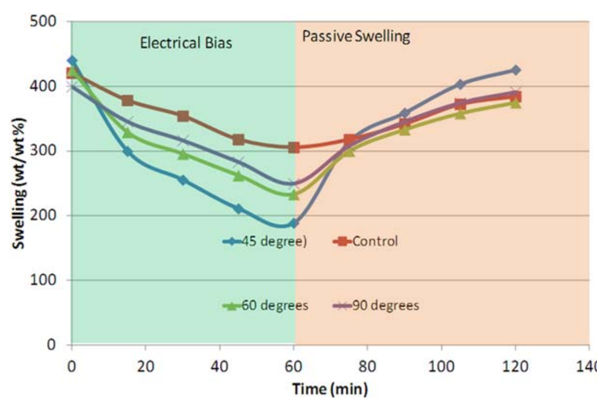

Figure 6. Swelling results for ERH with an applied pulsed (monophasic) electrical bias with different electrode spacing. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

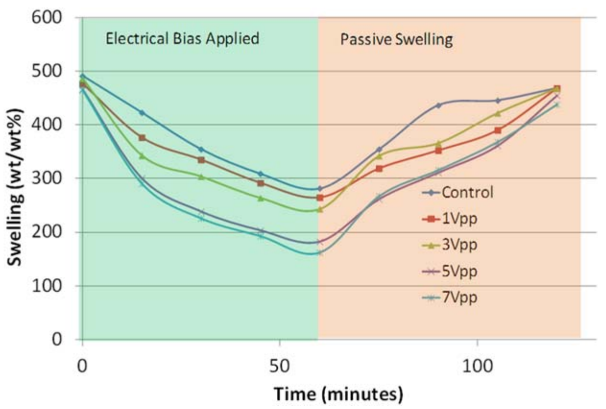

Figure 7. Swelling results for ERH with an applied pulsed DC electrical bias with different voltage amplitudes using 50% duty cycle and 1 kHz bias parameters. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

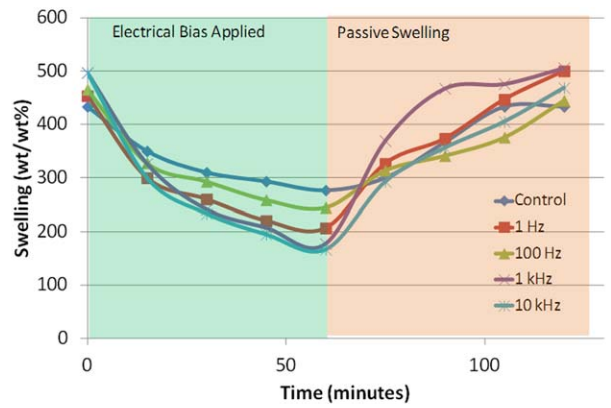

Figure 9. Swelling results for ERH with an applied pulsed DC electrical bias with different frequencies using 5 V and 50% duty cycle bias parameters. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

applied and the amount of time that 0 V is applied. A 100% duty cycle would represent a DC voltage. The deswelling results of varying the duty cycles is shown in Figure 8. The results demonstrate that increasing the duty cycle caused the deswelling to increase, which was expected since an increased duty cycle applies a bias for a longer duration. The 20%, 40%, and 60% duty cycle samples did not have any electrolysis or pH change. However, significant amount of electrolysis and pH change were seen for the 80% duty cycle samples. The difference in deswelling from 40% to 60% was minimal, but the 80% duty cycle samples had significantly more deswelling, this is due to multiple mechanisms of action of deswelling the ERH. The addition of electrolysis and pH change demonstrates that there were other factors that were influencing the deswelling of the ERH other than the applied electrical bias.

The deswelling results with varying applied electrical bias frequencies is shown in Figure 9. The results show that a pulsed DC electrical bias of 1 and 10 kHz had the most deswelling, but the difference between the two was not significant. On the other hand the 1 Hz electrical bias had significantly more deswelling when compared with the samples with 100 Hz stimulation. The reason for this is that with a 1 Hz electrical bias there was a significant amount of electrolysis and pH change [Figure 11(a)]. However, there was no electrolysis or pH change for samples with a 100 Hz applied electrical bias. Therefore the effects of adding more mechanisms that can cause deswelling lead to an increased shrinking of the ERH with 1 Hz electrical bias. The 100 Hz deswelling rates were similar to the control (unbiased) this is believed to be due to the affects from the relaxation time. From the impedance results the relaxation frequency for the ERH is 931 Hz, so an applied bias frequency lower than the relaxation frequency will allow the hydrogel to passively respond during the period of 0 applied voltage, which in this case would be a period of 50 ms. There is still some influence from the applied electrical bias as the samples did deswell more than the control, but the rates are lower than the 1 and 10 kHz values which are both above the relaxation frequency.

Based on the results presented the authors were able to combine the parameters to develop the optimal stimulation parameters. Two optimal stimulation parameters were developed (i) for biomedical applications (no electrolysis or pH change) and (ii) for

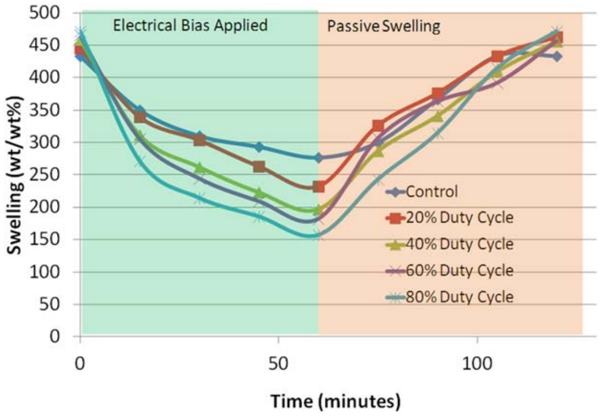

Figure 8. Swelling results for ERH with an applied pulsed DC electrical bias with different duty cycles using 5 V and 1 kHz bias parameters. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

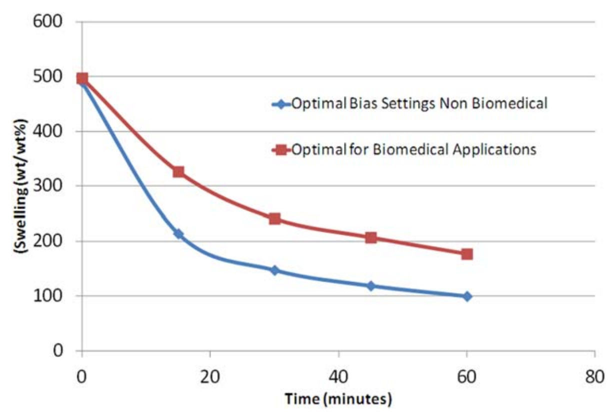

Figure 10. Swelling results for ERH using optimal bias conditions for biomedical and non-medical applications. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

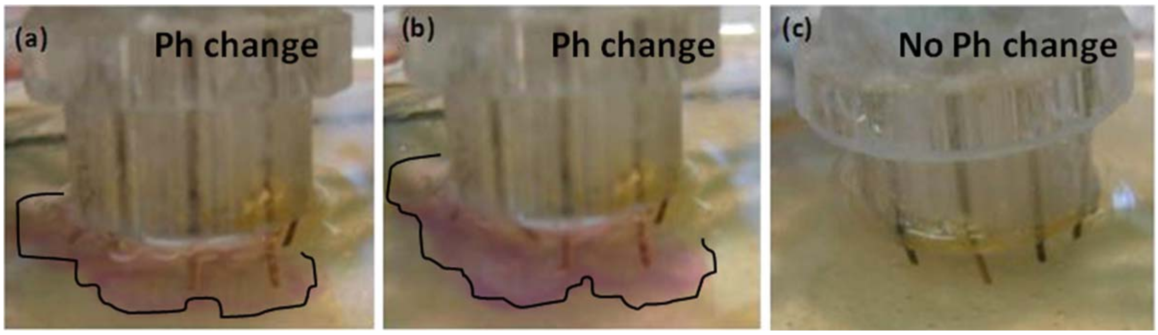

Figure 11. Pictures of electrical biasing of IDT electrodes using pH indicator solution (**a**) results using 1 Hz, 5 V, 50% DC shows significant color change in solution due to pH change and electrolysis, (**b**) optimal non-medical bias parameters (7 V, 80% DC, 10 kHz) shows significant color change in solution due to pH change and electrolysis, (**c**) results for optimal medical bias parameters (5 V, 50% DC, 1 kHz), no change in color or bubble formation. *Black line* shows the outline of the pH change. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

non-biomedical applications where pH change and electrolysis are acceptable. Both sets contained a monophasic pulsed DC waveform with 45° electrode separation (closer separation would likely result in higher deswelling). For medical applications the other parameters include 5 V peak to peak, 50% duty cycle, and 1 kHz frequency. For non-medical applications the parameters include 7 V, 80% duty cycle, and 10 kHz frequency. The average deswelling of the samples with these parameters is shown in Figure 10. The results show a significant difference between the two samples where the non-medical parameters decreased from 500% swelling to 100% swelling from the original mass, and the medical parameter materials went from 500% swelling to 177%. Figure 11(b) demonstrates that the parameters for the non-medical applications have a significant amount of electrolysis and pH change (shown by the change in color of the solution and air bubbles around the electrodes), which is not suitable for medical applications. However, Figure 11(c) demonstrates that the electrical bias parameters for the "medical" applications does not have significant pH change or electrolysis, as there was no change in color or air bubble formation.

The authors assessed the most significant factors for deswelling and assumed that there were no significant factor interactions. This assumption is validated by the results in Figure 10. However, some parameters are directly linked, for instance electrode spacing and voltage amplitude. One possible mechanism of action of ERH is that they respond to electric field changes, which would be directly linked to the spacing and the voltage. The mechanism of actions can be influenced by these interactions, for instance a high duty cycle combined with a high voltage causes pH change and electrolysis. The parameters for the optimal bias for a medical application were selected as they were the highest values without causing pH change or electrolysis.

A numerical model was developed based on all the experiments in order to predict the effects of varying the different parameters in order to predict deswelling rates in the future. The numerical model was developed from plotting the amount of shrinkage of each set of samples and determining a best fit model to the data. This is represented by the following equation:

$$D=\frac{2.76\ln(F)-0.003DC^2+0.66DC-0.448V^2+7.29V}{n} \tag{2}$$

The D is the amount of deswelling in %, F is the frequency in Hz, DC is the duty cycle in percentage, and V is peak to peak

Table I. Table Demonstrating the Accuracy of the Predicted versus Experimental Results for Shrinking

Voltage (V)	Duty cycle (%)	Frequency (Hz)	Predicted shrinkage (%) (Model)	Shrinkage (%) (experimental)	Percent error (%)
5	50	100	61.59	65.2	5.53
7	80	10,000	77.44	80.1	3.32
1	50	1000	45.29	45.5	0.45
3	50	1000	55.03	54.09	1.74
5	50	1000	61.59	60.88	1.17
7	50	1000	64.98	65.07	0.14
5	20	1000	49.82	47.86	4.10
5	40	1000	58.22	57.06	2.03
5	60	1000	64.42	60.88	5.81
5	80	1000	68.42	68.64	0.32
5	50	100	55.97	54.1	3.45
5	50	10,000	67.22	66.42	1.20

voltage in V, and n is a constant. The constant n has a value of 1.13, and is believed to be based on the interactions of the main effects. In order to validate the formula the modeled and experimental shrinkage values were compared as shown in Table I. The results show that all the values were within a 6% error. The numerical model is only valid for the experimental setup and solution concentrations used, if a different concentration of solution is used the values would need to be adjusted in order to predict the amount of shrinkage during 1 hour of applied electrical bias.

CONCLUSION

This article demonstrated the synthesis of an ERH and the effects of various electrical bias parameters on the deswelling rates of the PLMANa hydrogel. Each of the various electrical bias parameters were experimented with to determine the key parameters to maximize deswelling of the ERH for both biomedical applications and non-medical applications. A 3D IDT electrode configuration was used to conduct the experiments. The results showed each of the parameters had a significant effect on the deswelling of this particular ERH. The article also reports on the EIS of the ERH and determined that the relaxation time of the ERH is an important parameter when developing a frequency dependent electrical bias. The authors demonstrated that a Pulsed DC bias was the most optimal waveform for medical applications with a frequency above the relaxation frequency. Optimal electrical bias parameters were validated by combining the maximum deswelling parameters from the individual experiments, and testing the ERH for deswelling. A numerical model was developed so that future electrical parameter changes could be modeled for an accurate prediction of deswelling prior to experimental testing.

The results in this article were validated using the PLMANa ERH. Other ERH will have different optimal electrical bias parameters. However, as long as the mechanism of action of the different ERH is the same then the key parameters that influence deswelling should be the same. For instance, this article shows that frequency is an important parameter, and the optimal frequency is determined by the materials relaxation time, which will vary for each ERH. This article identifies the key electrical parameters that influence deswelling, but the individual parameters are material dependent, so each ERH would need to be tested in order to determine their optimal parameters.

Future work will be focused on the ERH and increasing the response time, currently most applications for ERH require quick actuation, and the ERH used in this article took an hour to reach maximum deswelling, which is not ideal for most medical applications. In addition novel microfabricated IDT electrodes that could be integrated onto a delivery system will be developed.

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