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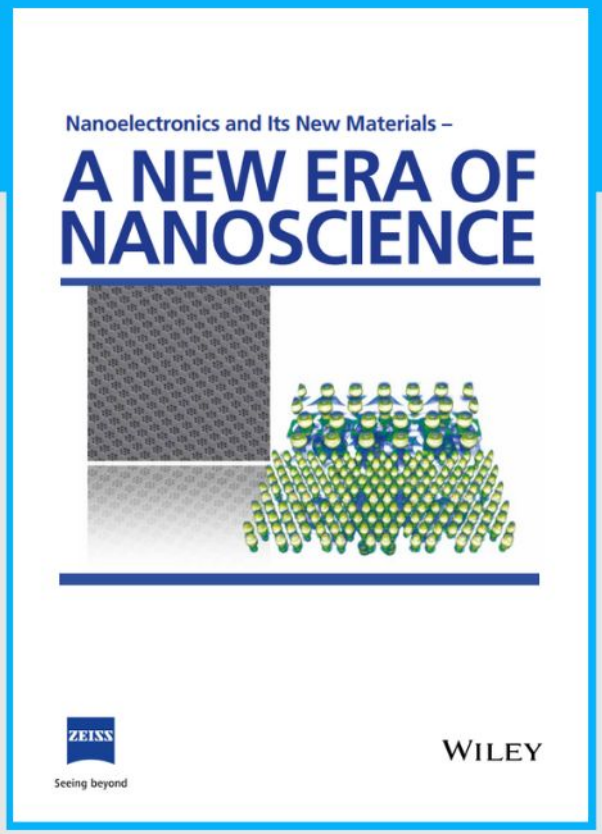

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Electrically Induced Bursting of Aqueous Capsules Made from Biopolymers: 'Switching On' the Release of Payloads

*Ankit Gargava, Wenhao Xu, and Srinivasa R. Raghavan**

The use of electric fields to stimulate the delivery of drugs or other active ingredients is of great interest for wearable electronics and other applications. Most attempts at electrically induced delivery with soft materials in water have focused on electronically conducting polymers (e.g., polypyrroles) or conductive nanocomposites (e.g., polymers with carbon nanotubes). Here, electrical responses are induced even in structures made from nonconducting biopolymers that are widely available, biocompatible, and biodegradable. The materials studied here are spherical capsules created from the anionic polysaccharide alginate by cross-linking with cations like Ca^{2+} or Cu^{2+}. When these capsules are placed in an aqueous solution and subjected to an electric field (direct current) of ≈8 V cm^{-1}, they deform within a couple of minutes and then burst and disintegrate into pieces within ≈5 min. Capsules across a range of length scales (200 µm to 2 cm) respond in the above manner, and the electroresponse persists even if the capsules are embedded in a non-ionic gel matrix. This electroresponse is due to electrophoretic migration of charged species (ions and/or polyelectrolyte chain-segments) within (or out of) the capsules. In an alginate capsule, the cations are induced to migrate away from the positive electrode, which creates a weakly cross-linked region of the capsule that swells appreciably. This anisotropic swelling continues until the capsule eventually bursts. Applications for electroresponsive capsules that highlight the spatial and temporal accuracy possible with an electrical stimulus are discussed. The bursting of capsules can be used to release solutes loaded inside these structures. Also, even the deformation of intact capsules can be used to create electrically actuatable valves, where a liquid flows out through the valve only when a capsule plug is dislodged.

1. Introduction

Soft materials filled with water are widely encountered in biomedical and consumer products. Two classes of such materials are hydrogels[1,2] and capsules.[3,4] A hydrogel is a water-filled network of polymer chains, with the network being formed by either covalent or physical cross-links between the chains.[1,2] A capsule is a spherical structure in which the core is either an aqueous solution or gel whereas the shell is a distinct layer.[3,4] In some cases, the shell can have the same chemistry as the core but a higher degree of cross-linking. In other cases, the shell can be a coacervate or even a covalently cross-linked layer whereas the core can be physically cross-linked. Two types of capsules that we have extensively studied in our lab are based on the common biopolymers (polysaccharides) alginate and chitosan.[5–8] Both gels and capsules find use in biomedical applications such as drug delivery and tissue engineering, as well as in soft robotics and wearable devices.[9–12]

In regard to gels and capsules, a recurring theme has been to make these structures responsive to external stimuli such as solution pH, salt concentration, temperature, light (at various wavelengths), and magnetic and electric fields.[2,4] In the case of a gel, it can be induced to swell or shrink in response to the above stimuli.[2,13] Alternatively, a bulk gel can be actuated to change its shape: for example, a flat sheet can fold into a pancake or tube in response to the same stimuli.[14,15] In the case of capsules, responses that can be induced include capsule inflation and bursting,[16] autonomous capsule motion,[17] capsule color changes,[5] or an abrupt change in capsule permeability.[18] Among the stimuli of interest, an emerging one is the *electric field*, which is particularly attractive because it can be easily turned on and off at a particular location (i.e., with spatial precision) as well as at a precise time (i.e., with temporal precision). Other stimuli such as pH, ionic strength, and temperature cannot achieve the same level of spatial or temporal precision. Light can do so under some cases, but light gets attenuated as it passes through many materials. Moreover, light sources are bulky whereas electric fields can be applied with just a battery (DC) or by connecting to the commercial AC electric supply. In turn, electrical stimuli can be exploited even

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in portable devices that can be controlled wirelessly and from remote locations, e.g., through the Internet (via Bluetooth).

Can soft materials placed in water be made to respond to an electric field? If so, what kind of materials exhibit such a response? Electroresponsive soft materials have typically been made using conductive polymers (CPs), such as polypyrroles and polythiophenes, where the charge carriers are electrons.[19–24] For example, drugs have been chemically conjugated to such CPs, and upon applying an electric current, the release of these drugs from the CPs has been triggered. Alternatively, instead of CPs, electronic conductivity has been imparted to soft materials by adding conductive nanoparticles such as carbon nanotubes (CNTs).[25] For instance, Yun et al. created capsules with CNTs in their shells and found that the capsules became more permeable under an electric field.[25] However, materials such as CPs and CNT-based composites have their limitations because they are either expensive or difficult to synthesize, and are generally not biodegradable or biocompatible. Note also that, for a response to occur in an electronically conductive material, it must be in direct contact with an electrode (i.e., the source of current).

An alternative to electrons is to rely on ions as the charge carriers. Polyelectrolytes, i.e., polymers with ionizable backbones, are widely available and are biocompatible. Hydrogels based on polyelectrolytes have been investigated in electric fields. (The hydrogels can be placed in solution either with or without direct contact with the electrodes before applying a current.) In some studies, bulk gels have been reported to shrink (or swell) under a field.[26,27] If such shrinking occurs non-uniformly, the gel can be also made to bend, and this bending can further be transduced into a slithering motion of the gel.[28–32] Several studies have also reported that gel films can be eroded by applying a field (all these films were in contact with one electrode).[33–36] Such erosion of gel films has been used to deliver drugs entrapped in the films. In addition, electrical response has also been reported for certain nanoscale polymer vesicles (formed by the self-assembly of special block copolymers or homopolymers) by exploiting their sensitivity to redox conditions.[37–39] To our knowledge, none of the papers noted above have investigated *spherical gels or capsules* made from polyelectrolytes. No significant transformations to such capsules by electric fields have ever been reported (such as bursting).

Here, for the first time, we show that a significant electroresponse is indeed possible in spherical gels and capsules made from common biopolyelectrolytes—including the anionic alginate and the cationic chitosan—that are widely used in biomedical applications. Capsules (with liquid or gelled cores) of these polymers, formed by noncovalent interactions, are placed in water and a moderate DC electric field (≈10 V cm^{-1}) is applied using remote electrodes (i.e., the electrodes do not touch the capsules). We observe that the capsules deform or swell anisotropically within a minute and then rapidly burst within ≈5 min, thereby releasing their internal contents. Capsules across a range of length scales (200 µm to 2 cm) respond in the above manner, and the electroresponse can be tuned by varying the field strength as well as the capsule composition. We propose a mechanism based on electrophoretic migration of charged species (ions and/or chain-segments) within (or out of) the capsules. Finally, we conclude by discussing applications. Electrically induced bursting of capsules could be used for the release of encapsulated payloads such as drugs, perfumes, or agrochemicals. Also, the same capsules could be used to create electroactuated valves, which open to allow liquid flow only when an electric field is switched on.

2. Results and Discussion

2.1. Preparation of Capsules

We study three types of spherical particles made from biopolymers, all of which we will refer to as 'capsules'. The implication is that, in each case, the particle core and shell are different in some way. The first such capsule (**Figure 1**A) is made from the anionic biopolymer alginate by dropping an alginate solution into a reservoir solution of multivalent cations such as Ca^{2+}, Cu^{2+}, Zn^{2+}, or Fe^{3+}.[7,8] Alginate chains become cross-linked by the cations into a gel-network (Figure 1A); note that the chains are bound by cations along 'egg-box' junctions.[8] If the droplets are incubated in the reservoir for a long time (≈10 min), the cross-linking will be uniform throughout the droplet. For shorter incubation times (≈5 min, which is more typical), the droplet core will be cross-linked less than the periphery,

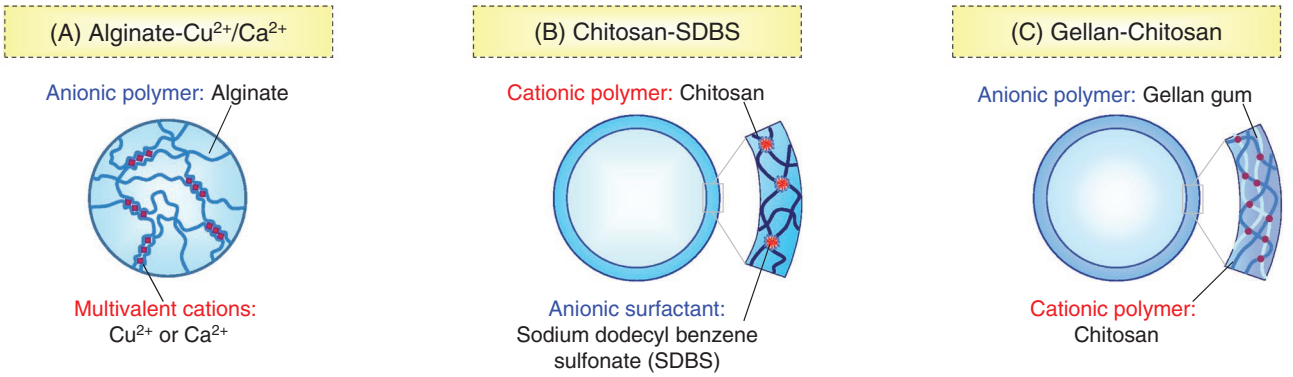

Figure 1. Biopolymer capsules evaluated in this study. Each capsule is created by combining an anionic or cationic polysaccharide with moieties of opposite charge. A) Polymer-ion capsules by cross-linking anionic alginate with multivalent cations (Cu^{2+} or Ca^{2+}). B) Polymer-surfactant capsules by combining cationic chitosan with the anionic surfactant SDBS. C) Polymer–polymer capsules by combining anionic gellan gum with cationic chitosan. In all cases, a solution of the polymer listed on the top is introduced as droplets into a reservoir containing the moiety listed on the bottom to form the capsules.

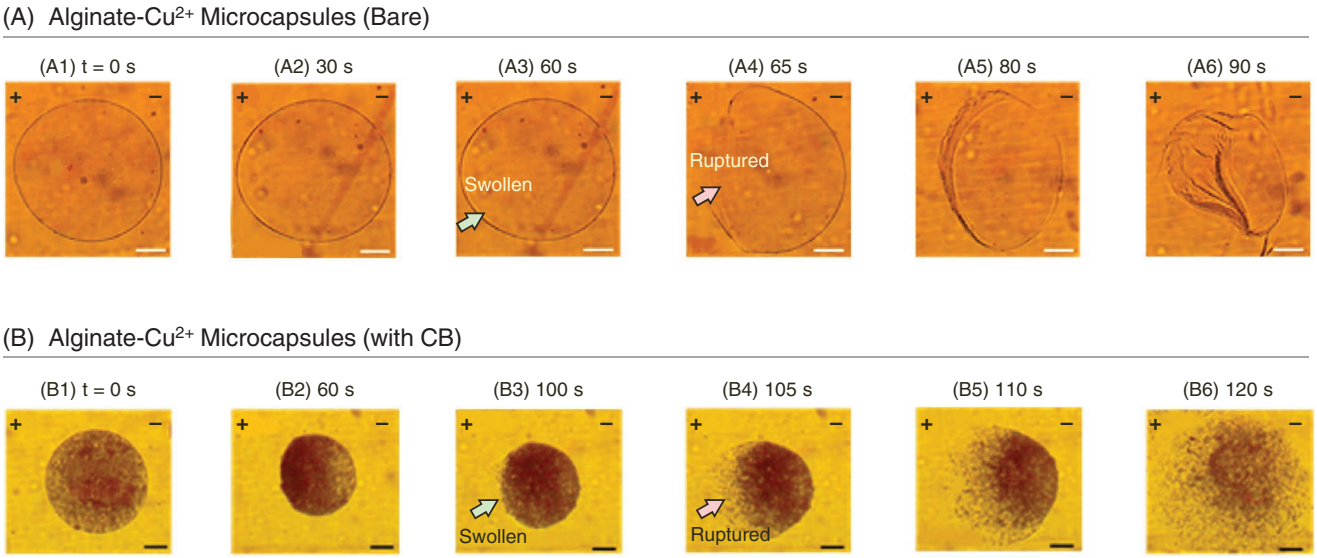

Figure 3. Electrical bursting of alginate-Cu^{2+} microcapsules over time. A) Bare microcapsule (with no internal payload). B) Microcapsule with carbon black (CB) nanoparticles. The CB helps in visualizing the rupture. In both cases, the microcapsules are placed in 10 mM NaCl solution and a DC voltage of 15 V is applied. Images are shown at different time points (the images in (B) are from Movie S1, Supporting Information). In both cases, the microcapsules swell on the side closer to the + electrode before rupturing on that side. Scale bars: 100 µm.

resulting in a core-shell structure, i.e., in a capsule. Alginate capsules (also sometimes termed 'beads', or simply 'gels') are usually formed with calcium (Ca^{2+}), but here we mainly use copper (Cu^{2+}) as the cross-linking cation because capsules of the latter are more stable and robust than those of the former.[15,40]

The second kind of capsule (Figure 1B) is made from the cationic biopolymer chitosan by adding its droplets into a solution of the anionic surfactant sodium dodecyl benzene sulfonate (SDBS). This results in capsules with a liquid core and a shell formed by electrostatic complexation (akin to coacervation) of the oppositely charged polymer and surfactant.[5] Lastly, the third kind of capsule (Figure 1C) is made by adding another anionic biopolymer gellan gum into a solution of the cationic polymer chitosan. Here again, the result is capsules with a liquid core and a shell featuring a coacervate of the oppositely charged polymers.[6] The capsules in Figure 1 have been deliberately chosen as representative examples for three distinct modes of physical cross-linking, involving: A) a polymer and multivalent ions of opposite charge;[8] B) a polymer and an oppositely charged surfactant;[5] and C) two oppsitely charged polymers.[6]

The above capsules were prepared over a range of sizes, which for simplicity we will classify as being in the macroscale (> 1 mm) or the microscale (< 1 mm). In the case of macroscale capsules, droplet sizes were controlled using plastic pipettes or syringe needles with different gauges.[5,6] To prepare microscale capsules, on the other hand, we used a microfluidic setup previously developed in our lab that has been described in detail elsewhere.[7,8] A key distinguishing feature of this setup is the use of gas as the continuous phase instead of oil.[8] Pulses of compressed air or nitrogen gas are used to shear off aqueous microdroplets from a capillary tip. The microdroplets are then added to a reservoir solution, as before, where they are converted to microcapsules. The microcapsule size is controlled by the feed flow rate and the frequency of gas pulses.[8]

2.2. Electrical Bursting of Capsules

We studied capsules under an electric field using the setup shown in **Figure 2**. The capsule is placed in a test solution and graphite electrodes are placed on either side, with the anode (positive electrode) on the left and the cathode (negative electrode) on the right. This orientation of the capsule relative to the electrodes will become important in analyzing the results. **Figure 3** shows the first set of results, which are for Cu^{2+}-cross-linked alginate microcapsules (200 µm radius) in a 10 mM NaCl solution. A voltage of 15 V (field strength of 8 V/cm) is applied across the test cell at $t = 0$, and the microcapsules are observed through an inverted optical microscope. The images in Figure 3A are for empty microcapsules whereas those in

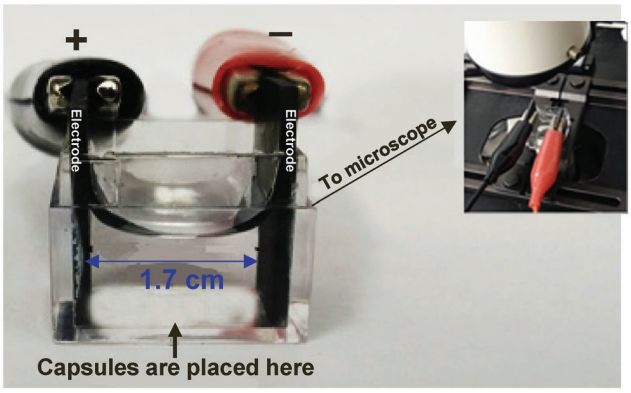

Figure 2. Setup used to study the electrical response of capsules. Capsules are placed in a rectangular cell containing an aqueous solution (typically this is 10 mM NaCl). The cell is flanked by two graphite electrodes, which are connected to the + and − terminals of a DC power source. The cell is placed on an inverted microscope for close observation of the capsules in the presence of the field.

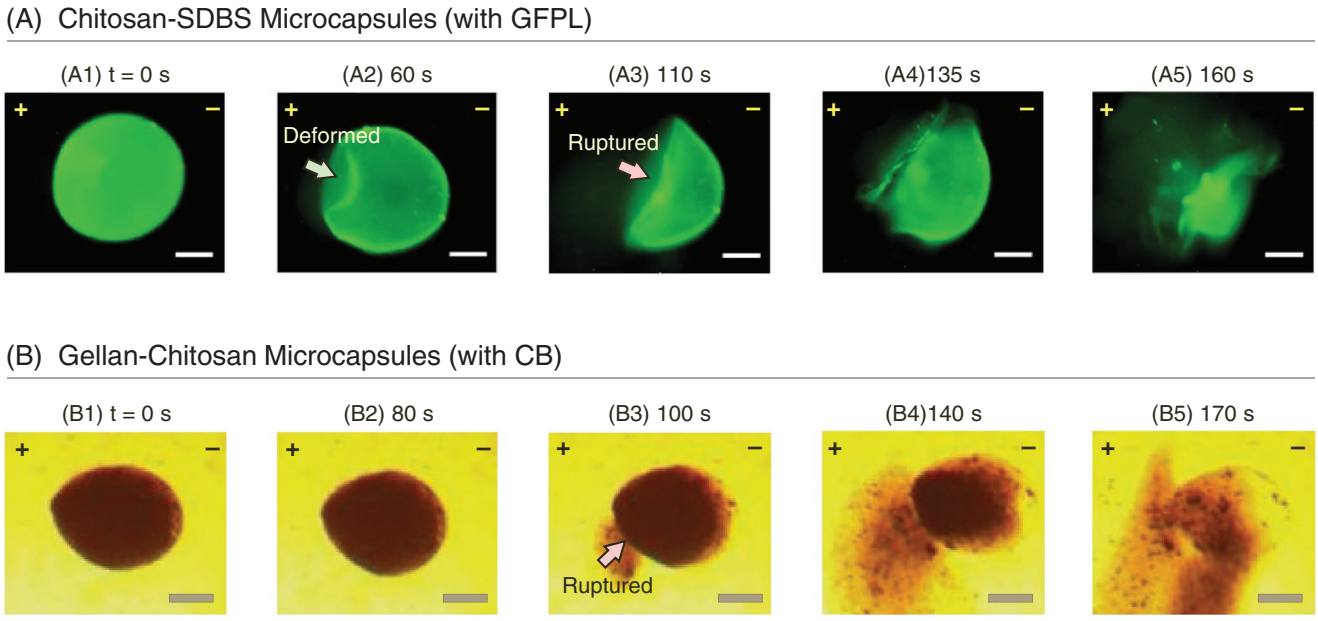

Figure 4. Electrical bursting of two microcapsule types over time. A) Chitosan-SDBS with green-fluorescent polystyrene latex (GFPL) nanoparticles. B) Gellan-chitosan with CB nanoparticles. In both cases, the microcapsules are placed in 10 mM NaCl and 15 V DC is applied. Images are shown at different time points (the fluorescence images in (A) are from Movie S2, Supporting Information). In both cases, the microcapsules rupture on the side closer to the + electrode. Scale bars: 100 µm.

Figure 3B are for microcapsules with 0.5% of carbon black (CB) nanoparticles dispersed in their core. The CB can be considered a model payload and its presence aids in visualization. As long as the capsule stays intact, the CB remains sequestered in the core.[6,8] Both sets of images show preferential swelling of the microcapsule on its left side (nearer the + electrode) (Photos A3 and B3) after about a minute of applying the field. The swelling can be clearly seen in Photo B3 because the CB in the microcapsule gets diluted as the left side swells (i.e., this side looks more transparent). Once the swelling starts, it continues for the next 10–20 s until the left side of the microcapsule suffers a rupture (Photos A4 and B4). The final collapsed microcapsule looks like a deflated balloon in Photo A6. In Photo B6, the rupture of the microcapsule induces the payload (CB nanoparticles) to burst out and spread all over the microscopic field of view.

Figure 4A shows the response of a chitosan-SDBS microcapsule (200 µm radius) to the same 15 V voltage. The microcapsule contains 0.5% green-fluorescent polystyrene latex (GFPL) nanoparticles dispersed in its core, and the images are taken with a fluorescence microscope. In this case, around the 60 s mark (Photo A2), the left (+) side of the capsule appears to bend and fold inward. Thereafter, at ≈110 s (Photo A3), this side breaks and the contents then spill out into the solution. Next, Figure 4B shows a gellan-chitosan microcapsule (200 µm radius) with 0.5% CB nanoparticles. When subjected to a 15 V field, a break in the left (+) side of the capsule shell is first seen at around the 100 s mark (Photo B3). This break grows over the next 60 s and the capsule completely disintegrates. In the process, the CB nanoparticles again spill out of the capsule and spread all over the solution. Thus, the net result is the same for all three kinds of capsules studied in Figures 3 and 4—they all burst apart within a couple of minutes of switching on the electric field.

Electrically induced disintegration thus appears to be a widespread effect in capsules assembled by physical interactions. To show the generality of this phenomenon, we repeated the above experiments with multiple capsules in a couple of different ways. First, we placed a number of alginate-Cu^{2+} microcapsules in a 10 mM NaCl solution and applied the 15 V field. As shown in **Figure 5**A, all the capsules swell on their side closer to the + electrode and eventually break at this side within 7 min. The capsules do not all break at the same instant of time, and there is no particular pattern or order to their breaking (e.g., distance

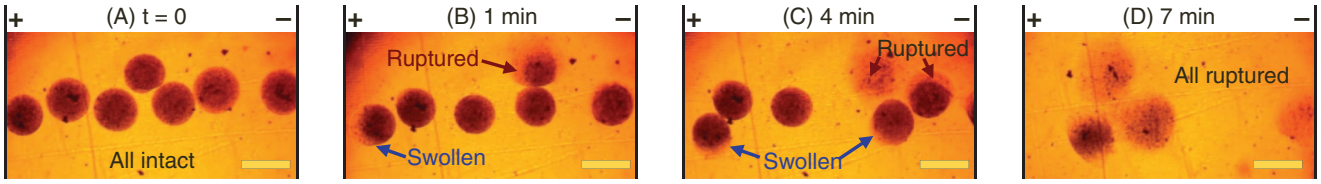

Figure 5. Electrical bursting of a batch of alginate-Cu^{2+} microcapsules. The microcapsules are placed in 10 mM NaCl solution and 15 V DC is applied. Images of several microcapsules (all with CB) are shown at different time points (the images are from Movie S3, Supporting Information). All microcapsules swell on one side and rupture, as shown previously in Figure 3. Scale bars: 300 µm.

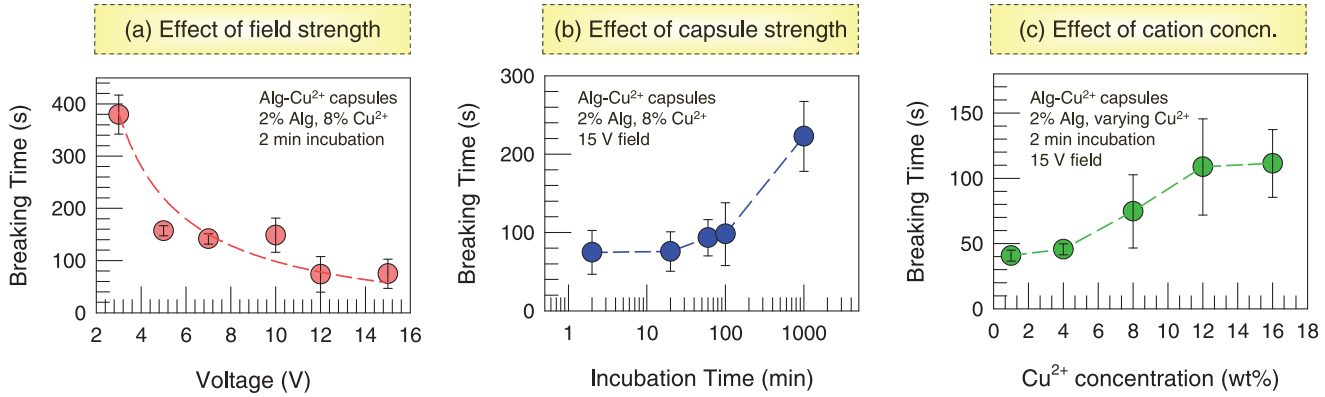

Figure 6. Effects of different variables on the electrical rupture of alginate-Cu^{2+} microcapsules. Microcapsules (with CB) are placed in 10 mM NaCl and a DC voltage is applied. The breaking time is the time at which the capsule first shows a rupture (as seen from the release of CB). A) Effect of varying the voltage (all capsules made by adding 2% alginate to 8% Cu^{2+} and incubating for 2 min). B) Effect of incubation time (all capsules made by adding 2% alginate to 8% Cu^{2+} and incubating for different lengths of time). The longer the incubation, the stronger the capsule. C) Effect of Cu^{2+} concentration (all capsules made by adding 2% alginate to varying Cu^{2+} and incubating for 2 min). The higher the Cu^{2+}, the more cross-linked the capsule. Lines in all plots are to guide the eye. For each data point, at least three samples were studied and the data shown are the mean values. Error bars correspond to standard deviations.

to either electrode is not a factor). This was verified through different trials similar to the one shown in Figure 5A. In another variation, we placed multiple capsules in a gel before applying the field. For this, alginate-Cu^{2+} microcapsules were combined with a hot solution of the biopolymer agarose and then cooled. The result was an agarose gel with the capsules entrapped in the gel. The gel was cut into a 1-cm cube, which was placed in a 10 mM NaCl solution. When the 15 V field was applied, all the capsules still broke within ≈7 min in the same manner as in Figure 5A. Because capsule breakage is unaffected by the distance to either electrode, we conclude that electrochemical reactions at the electrodes are unlikely to be responsible for the phenomenon.

2.3. Effects of Different Factors on Capsule Bursting

From the above observations, we can roughly estimate the breaking time of a microcapsule, i.e., the time at which we first detect a rupture by optical microscopy. We now discuss the effects of different variables on this breaking time. All the experiments were done on alginate-Cu^{2+} microcapsules. First, we varied the applied voltage. **Figure 6**A reveals a monotonic decrease in breaking time with increasing DC voltage. No rupture of the capsules was observed below 3 V (field strength of 1.8 V cm^{-1}). The breaking time was ≈6 min at 3 V, ≈150 s at 5 V and it dropped to ≈70 s for 15 V. Most of the data in this paper for capsule breaking was collected at 15 V (field strength of 8 V cm^{-1}) for convenience. We also studied the capsules under a sinusoidal (AC) field with an amplitude of 15 V and a frequency of 50 Hz. No swelling or rupture of the capsules was observed in this case.

Next, we varied the parameters influencing the structure of alginate-Cu^{2+} capsules. These capsules are prepared by dropwise addition of 2% alginate into a solution of Cu^{2+} (typically 8%). As a liquid drop stays in the Cu^{2+} solution, it gets converted into a solid capsule. The time the drop remains in the Cu^{2+} solution before being washed is the incubation time (typically, this is held at 2 min). The longer this time, the higher the density of cross-links between alginate chains and Cu^{2+} ions, and thus the stronger the capsule.[15,40] (Also, with a longer incubation time, the cross-linking will be more uniform throughout the droplet, resulting in less variation between the capsule core and shell.)[8] Figure 6B plots the breaking time of capsules under a 15 V field as a function of the incubation time in an 8% Cu^{2+} solution. We find that the longer the incubation time, the higher the breaking time. Thus, stronger capsules take longer to break, which makes sense. We also varied the Cu^{2+} concentration in the solution from 1 to 16 wt%, with the incubation time fixed at 2 min. The breaking time under a 15 V field increases with increasing Cu^{2+} concentration (Figure 6C). Increasing the Cu^{2+} is expected to add cross-links and thus make the capsules stronger,[15,40] which is again consistent with their taking longer to break.

Another variable is the capsule size, which as mentioned above can be varied from the micro to the macroscale. Figure S1 (Supporting Information) shows the electrical response exhibited by macroscale capsules of A) alginate-Cu^{2+}, B) chitosan-SDBS, and C) gellan-chitosan. All the capsules have radii ≈2 mm (which is ≈10× larger than their microscale counterparts). For the experiments, the capsules were placed in a 10 mM NaCl solution and 15 V was applied. All the capsules break due to the electric field, similar to their microscale counterparts. The alginate-Cu^{2+} macrocapsules first swell and then break on their side near the + electrode (Figure S1A, Supporting Information), similar to the corresponding microcapsules (Figure 3B) and in approximately the same time. The gellan-chitosan macrocapsules (Figure S1C, Supporting Information) break in a similar manner to their microscale versions (Figure 4A), but they take longer to do so. But none of the macrocapsules completely disintegrate even after prolonged time in the electric field, which is different from the behavior of the microcapsules.

Alginate capsules can be formed by cross-linking with several multivalent cations,[15,40] and cation type was the next variable we studied. We tested macroscale alginate capsules formed

using Cu^{2+} (our typical case), as well as calcium (Ca^{2+}), zinc (Zn^{2+}), iron (Fe^{3+}), aluminum (Al^{3+}) and holmium (Ho^{3+}). All capsules were formed by dropping 2% alginate into 8% solutions of the respective cations and incubating for 2 min. The breaking time of each capsule under a 15 V field is plotted in Figure S2 (Supporting Information). Capsules with divalent cations as the crosslinkers (Cu^{2+}, Ca^{2+}, Zn^{2+}) all broke within 5 min. In the case of trivalent cations, capsules cross-linked with Ho^{3+} broke within 5 min while Al^{3+}-cross-linked ones took >10 min to break. However, Fe^{3+}-cross-linked capsules did not break even after 1 h under the field. Thus cation type significantly influences the electrical response of alginate capsules.

All the experiments reported thus far have been done with 10 mM NaCl as the background electrolyte. We also studied the breaking of alginate-Cu^{2+} capsules in the absence of salt, i.e., in deionized (DI) water. In that case also, the capsules ruptured when subjected to a voltage of 15 V, but it took longer (> 15 min) compared to the baseline results. In the absence of salt, the current recorded during the test is very low due to the low ionic conductivity of the solution. We then tried 1 and 100 mM NaCl, but there was no significant difference in the breaking time compared to the 10 mM case. One reason to avoid high NaCl concentrations is that alginate-Cu^{2+} capsules slowly disintegrate due to exchange of Cu^{2+} with Na^{+} ions.[40] Based on all these findings, we chose to perform all the other tests with capsules in 10 mM NaCl solutions.

2.4. Mechanism for Electrical Disintegration of Capsules

A crucial question from this study is why capsules break under an electrical stimulus. Analyzing electrical effects in our system is very complex as it requires an integration of knowledge from polymer physics, electrochemistry, colloid science, and thermodynamics. Before we present our hypothesis, it is worth mentioning other relevant results. We had shown that alginate capsules could be ruptured by an electric field even when embedded in an agarose gel. Agarose is a nonionic biopolymer that forms gels upon cooling a hot sol. Spherical gels of agarose (macroscale, ≈2 mm radius) can be made by dropping a hot agarose solution into a cold reservoir. When these gels are tested in a 15 V field, they remain intact. This implies that the polymer chains in a capsule or gel must be *charged* (i.e., should be *polyelectrolytes*) for electrical rupture to be seen. We also tested capsules formed by contacting chitosan with glutaraldehyde (GA). These capsules do not rupture in a 15 V field. In these capsules, GA forms *covalent bonds* between amines on adjacent chitosan chains. Evidently, these covalent bonds are too strong to be broken by an electrical stimulus. We conclude that electrical rupture only occurs in capsules formed by weak, physical bonds of an ionic or electrostatic nature.

Given that polyelectrolytes and electrostatic interactions are present in our capsules, could pH changes be responsible for their response? The case of pH dovetails with an electrochemical mechanism.[31] That is, when we pass a current through our solution at the voltages studied, water will get electrolyzed, and in turn, a pH gradient will be generated in the solution. The pH will be lowered at the anode (+) due to generation of H^{+} ions near it and conversely, higher at the cathode (–). What would happen when this pH wave reaches the capsule? Taking the case of an alginate capsule, we would expect the left (+) side of the capsule to experience a lower pH than the right (–) side. The low pH should make the left side shrink; however, the opposite is observed where this side swells before breaking. Also, we studied alginate-Cu^{2+} capsules in solutions of different pH without an electric field. No changes are seen at high pH, while there was some shrinking of the capsules at low pH. In no case did the capsules break simply due to pH. Note also that distance to the electrode(s) did not influence capsule breakage (Figure 5). All in all, an electrochemical mechanism (either due to changes in pH or other electrochemical reactions) cannot explain the breaking of our capsules.

We also considered ionic strength and osmotic effects.[32] As noted earlier, alginate-Cu^{2+} capsules show electrical rupture regardless of the salt (NaCl) concentration. For comparison, in the absence of the field, if an alginate capsule is placed in a concentrated (> 100 mM) salt solution, the capsule will shrink within a few minutes. If placed back in DI water, the capsule will swell back to its original size. This swelling and shrinking are due to differences in osmotic pressure (i.e., the total concentration of ions and molecular species) between the capsule lumen and the external solution. But these osmotic gradients seem to be insufficient to break the capsules. Overall, if electrical rupture was solely related to osmotic pressure or ionic strength, one would need to explain why these quantities would change sharply upon applying the field. As such, we can rule out these possibilities as well.

We now postulate a mechanism for the observed electrical rupture of our capsules (**Figure 7**). All the capsules have polyelectrolytes (cationic or anionic) and cross-linking molecules of the opposite charge. We will focus our explanation on alginate capsules, which is our most studied system. In these capsules, anionic alginate chains are cross-linked by multivalent cations like Cu^{2+} or Ca^{2+}. When placed under an electric field, we hypothesize that the cations will be pulled by electrostatic forces toward the cathode (–) (i.e., toward the right in Figure 7A).[36,41] Equivalently, the alginate chains will also be pulled toward the anode (+),[41] but because these chains are much larger than the ions, their mobility will be lower and ignored for our discussion. Next, we suggest that the electrostatic forces on the cations will be sufficient to exceed the strength of their ionic bonds with alginate chains. If so, the cations will be pulled out of their 'egg-box junctions' and will then electrophoretically migrate and redistribute themselves within a capsule. This will have a dual effect: on the left (+) side of the capsule, the cations will be depleted whereas they will be enriched on the right (–) side. Eventually, some cations may leak out of the capsule at the right edge. The depletion of cross-links on the left (+) side will *first induce that side of the capsule to swell* (as shown by the schematic in Figure 7B), which is what we observed experimentally in Figure 3. As the electrophoretic migration of cations continues, the removal of cross-links will *eventually cause the capsule to break and disintegrate* (Figure 7C), which is again consistent with the results in Figure 3.

How could we prove the above mechanism? We had suggested that some cations might escape out of the capsule under an electric field, and this can be tested experimentally. For this, we used alginate-Ca^{2+} capsules and eriochrome black T (EBT), a well-known colorimetric indicator for Ca^{2+}.

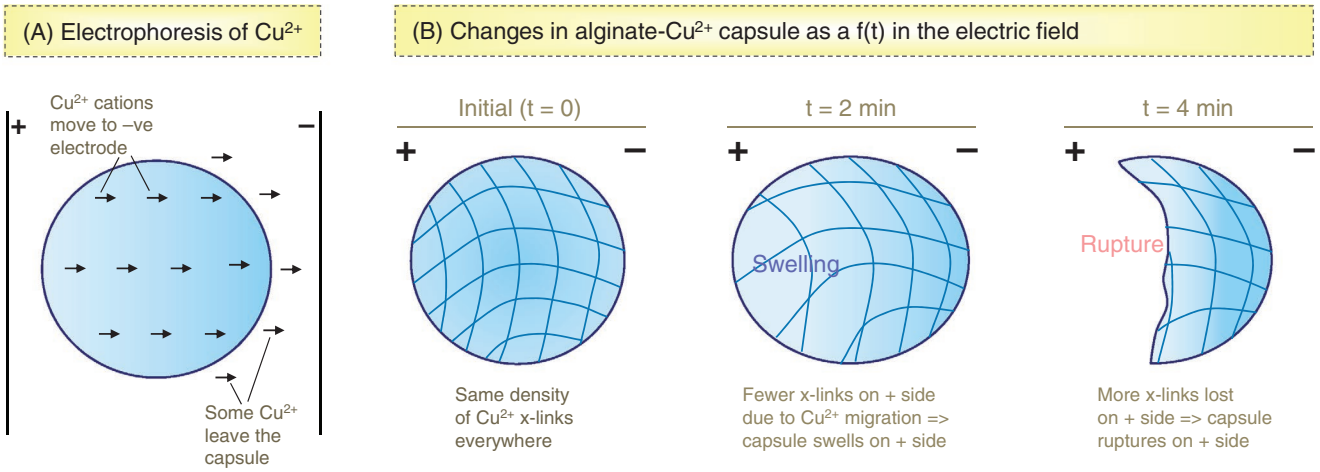

Figure 7. Mechanism for electrical bursting of alginate-Cu^{2+} capsules. A) The key is hypothesized to be the electrophoresis of charged species, in this case Cu^{2+} cations, which will migrate toward the –ve electrode. Such migration within the capsule will create zones that are enriched or depleted in these cross-linking ions. Some cations are also expected to be released out of the capsule. B) Changes in a single capsule are shown schematically. The side near the +ve electrode will have a lower Cu^{2+} concentration, and the depletion of cross-links (increase in mesh size) will induce this side to swell. Such swelling will continue until this side of the capsule eventually ruptures.

An ammonia-buffered solution of EBT is blue, but as Ca^{2+} is added, the solution turns from blue to violet to red (Figure S3A, Supporting Information). We placed five alginate-Ca^{2+} macrocapsules in our test cell with 2 mL of 10 mM NaCl solution (Figure S3B, Supporting Information). The capsules were over-cross-linked by 24 h incubation in Ca^{2+} so that they would not break in the field. Then we switched on the field at different voltages, after which 1 mL was quickly withdrawn from the test cell (i.e., from around the capsules) and mixed with EBT and ammonia (Figure S3B, Supporting Information). In the case of the negative control, i.e., capsules in the test cell for 10 min with no voltage, the EBT solution has a blue color, implying that the external Ca^{2+} is <1 mM (Tube 1). Next, a voltage of 6 or 7 V was applied for 10 min. The EBT solution now turns from blue to violet (Tubes 2,3), indicating a slight increase in external Ca^{2+} to ≈2 mM. The voltage was then increased to 15 V for 10 min, and in this case, the EBT solution turns light-red (Tube 4), corresponding to ≈7 mM of external Ca^{2+}. The EBT results thus support our hypothesis that the electric field breaks alginate-Ca^{2+} cross-links and induce some of the Ca^{2+} to leave the capsules into the external solution. This eventually leads to capsule rupture.

We suggest that the same mechanism for electrical rupture also applies to chitosan-SDBS and gellan-chitosan capsules. In those cases too, the electric field will exert forces in opposite directions on the cationic and anionic species in the capsules. In chitosan-SDBS capsules, the SDBS surfactants are relatively small and comparable to the cations in alginate capsules. In gellan-chitosan capsules, both the constituents are polymers, but they are expected to be confined to a thin shell. Both these capsules have a liquid core whereas alginate capsules have a gelled core (Figure 1). Thus, the differences in electrical responses between the three systems studied here can be broadly attributed to: a) the sizes of their constituents, i.e., polymers versus small molecules; b) the strength of interactions between the oppositely charged constituents; and c) the morphology of the capsules (i.e., whether the core is liquid or gelled and the thickness of the shell). Larger molecules will migrate slower under the field, but if they are confined to a thin shell, they will only need to be dislodged by a short distance for the capsule to break. More study is needed to further clarify these differences and the relative contributions of (a) to (c). We also note that not all capsules will break under the field, one example being alginate-Fe^{3+} (Figure S2, Supporting Information).

2.5. Electro-Actuated Valves Based on Capsules

Electrical disintegration can be used to release payloads encapsulated in the capsules such as therapeutics or agrochemicals. Examples of such payload release have been shown in Figures 3B, 4B (CB particles), and Figure 4A (fluorescent particles). Another mode of electrically activated release is demonstrated in **Figure 8**, and in this case, the capsules do not have to be destroyed for release to occur. Figure 8A shows a macroscale alginate-Cu^{2+} capsule squeezed into the narrow end of a plastic transfer pipette. From the other end, the pipette is filled with water containing a model solute (a pink dye, Rhodamine B). This pipette assembly is then placed between electrodes in the test cell, with 10 mM NaCl (colorless solution) surrounding the pipette. Initially, the capsule blocks the downward flow of the pink fluid, i.e., the 'valve' remains closed. When 15 V is applied, within ≈3 min, the capsule deforms and breaks (Figure 8B). Thereby, the valve opens, releasing the pink fluid into the cell, where it mixes with the colorless NaCl solution. A key point is that if the capsule is not squeezed tightly in the pipette, it will still block the flow—then, even a slight deformation of the capsule by the field will dislodge the capsule and thereby open the valve. If the field is switched off at this stage, the capsule would be intact, but the actuation of the valve would still have occurred.

We extended this electro-actuated valve design to incorporate three valves (**Figure 9**A). Each valve features a pipette bearing a red fluid (Rhodamine 6G in water), with its narrow end blocked by an alginate capsule. The three pipettes are placed next to each

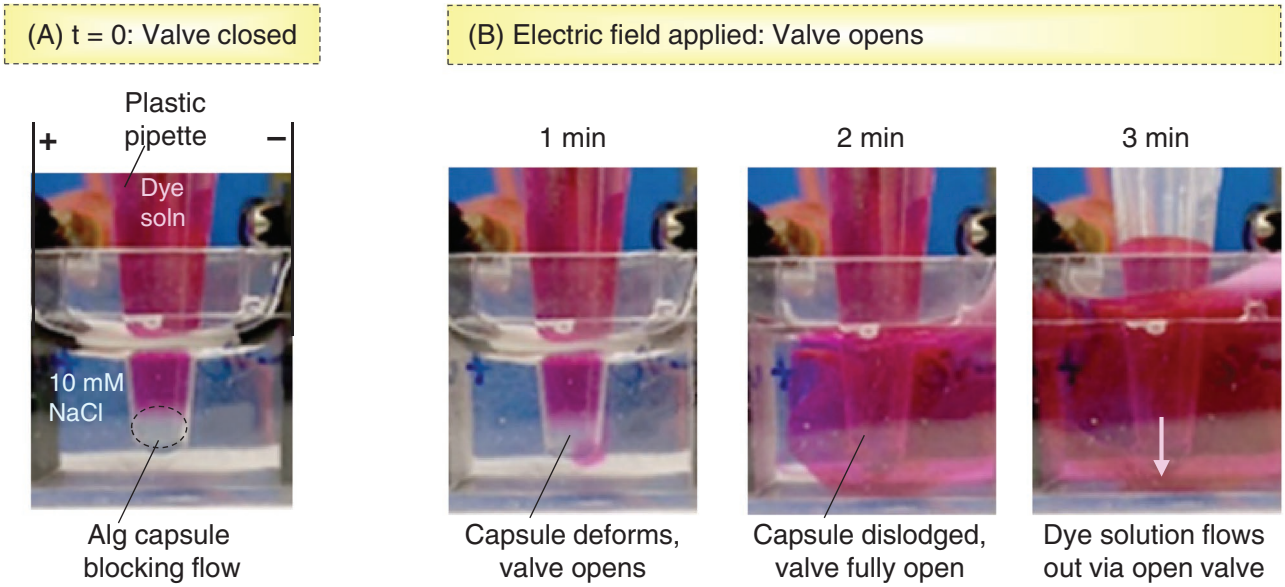

Figure 8. Electro-actuated fluid valve. A) An alginate capsule is wedged in at the end of a plastic transfer pipette to block the gravity-driven downward flow of a dye solution. The assembly is placed between two electrodes and the closed end is immersed in 10 mM NaCl. B) When the electric field (15 V DC) is applied, the capsule deforms within 1 min, thereby opening the valve. Thereafter, within 2 min, the capsule gets dislodged and the valve is fully opened, allowing the dye solution to flow out. The images in (B) are from Movie S4 (Supporting Information).

other in the same water-filled cell, and each pipette is flanked by a pair of graphite electrodes. This design allows us to actuate each valve independently. Initially, all three valves are closed, and the fluid in the cell is colorless (Figure 9B). We first apply a voltage of 15 V across Valve 3 (Figure 9C) by biasing the two electrodes on either side of the pipette. This dislodges the capsule and thus opens the valve, causing the red fluid to flow down into the collecting cell. Valves 1 and 2 are still closed at this stage because there is no voltage across them. Next, we apply 15 V across Valve 1, which opens this valve and releases the red fluid contained in it. Valve 2 is still closed at this point. Finally, we apply 15 V across Valve 2 and induce this valve to also open. The above sequential opening of valves demonstrates several features that could be useful for applications such as drug delivery. For example, the three valves can correspond to three doses of a drug. We can administer one dose at a time at regular intervals, or if a higher dose is desired, we can open multiple valves at the same time. Also, we can electrically actuate one valve without affecting other ones, which is difficult to achieve with other stimuli like temperature and pH. Thus, our setup shows the advantages of an electrical stimulus in terms of spatial precision (ability to be directed at a specific location) and temporal precision (ability to be switched on at a precise instant in time).

3. Conclusions

In conclusion, this paper reports a surprising result: that electric fields can induce a dramatic response in soft materials made from nonconducting biopolymers. The materials we study are capsules made from alginate, chitosan, and gellan gum, all of which are charged polysaccharides and are biocompatible and biodegradable. Each capsule is formed by cross-linking biopolymer chains via physical (ionic/electrostatic) interactions. Our principal finding is that, under a DC electric field (8 V/cm), all these capsules rupture and disintegrate in a span of <5 min. The mechanism for this electroresponse is attributed to electrophoretic rearrangement of ions and/or polyelectrolyte chains in

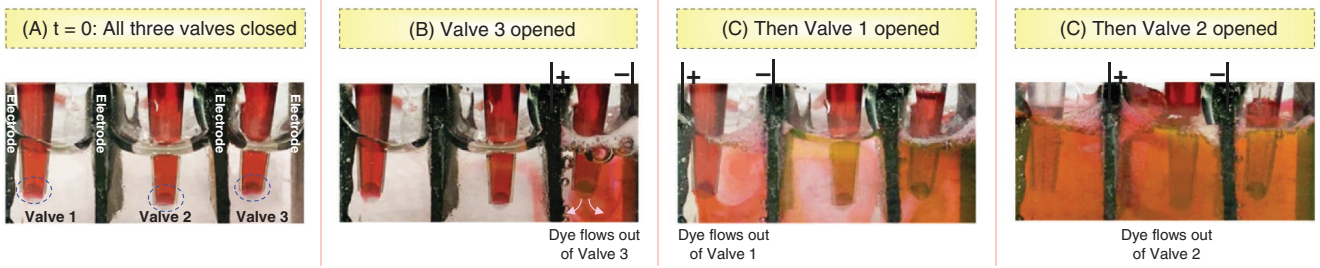

Figure 9. Sequential actuation of three valves by spatial and temporal control of the electric field. Each valve comprises a transfer pipette bearing a dye solution, with an alginate capsule at the end blocking the flow. The pipettes are flanked by graphite electrodes and the pipette ends are in 10 mM NaCl. A) All valves are closed. B) Valve 3 is opened by applying 15 V across it. C) Next, similarly, Valve 1 is opened. D) Finally, Valve 2 is opened.

the capsule. In the case of alginate capsules, they first swell anisotropically on their side closer to the anode (+ electrode). This is explained by the migration of cations away from the anode, thereby lowering the crosslink density on that side. As further cross-links are lost from the anode side, the capsule eventually breaks. Capsules formed by covalent bonds do not show such an electroresponse. Electroresponsive capsules can be used for electrically triggered delivery of solutes. A valve design is put forward where an orifice is blocked by a capsule and the valve is opened when the capsule is dislodged by the field. Future studies will focus on integrating these valves into remote-controllable devices made entirely from soft, biocompatible materials. Such devices could ensure that release of drugs or other active ingrdients can be switched on at a desired time and place.

4. Experimental Section

Materials: Most of the chemicals were purchased from Sigma–Aldrich. This included three biopolymers: alginate (medium viscosity alginic acid, sodium salt from brown algae), chitosan (medium molecular weight), and agarose (type I-A, low EEO); and the salts: copper chloride ($CuCl_2$•$2H_2O$), calcium chloride ($CaCl_2$•$2H_2O$), aluminum sulfate ($Al_2(SO_4)_3$•xH_2O), zinc sulfate ($ZnCl_2$•$7H_2O$), holmium chloride ($HoCl_3$•$7H_2O$), and sodium tripolyphosphate (TPP). Other chemicals included sodium hydroxide (NaOH, in pellet form), glutaraldehyde (GA, 50% in water), and the dyes Eriochrome Black T (EBT), Rhodamine B (RB), and Rhodamine 6G (R6G). Iron chloride ($FeCl_3$, anhydrous) was purchased from Acros Organics, acetic acid (CH_3COOH, glacial) from Fisher Scientific, sodium chloride (NaCl) from EMD Millipore, hydrochloric acid (HCl) from BDH, and ammonium hydroxide from J.T. Baker. The surfactant sodium dodecylbenzenesulfonate (SDBS, hard type) was from TCI America, while the biopolymer gellan gum (Kelcogel F) was from CP Kelco. Graphite sheets (3 mm thickness) were from Saturn Industries. Carbon black (CB) nanoparticles (N110) were from Sid Richardson Carbon Company. Green-fluorescent polystyrene latex (GFPL) nanospheres (diameter ≈100 nm) were from Polysciences. Deionized (DI) water was used to prepare aqueous solutions.

Macrocapsule Synthesis: To prepare alginate capsules, a feed solution of 2% of alginate in DI water was dropped into a reservoir solution containing multivalent cations, with a typical solution being 8% $CuCl_2$. The incubation time in the reservoir was typically 2 min. After this time, the capsules were removed, washed with DI water, and stored in a 10 mM NaCl solution or in DI water. To prepare chitosan capsules, a feed of 2% chitosan in 0.2 M acetic acid was dropped into a reservoir solution of 5% SDBS, where it was incubated for 3 to 5 min, then washed and stored as above. To prepare gellan-chitosan capsules, a feed of 1% gellan gum in DI water was dropped into a reservoir of 1% chitosan in acetic acid. After a 3 min incubation, the capsules were washed and stored as above. In all the above cases, the size of the capsules was dictated by the size of the feed droplet, which was varied by using either plastic transfer pipettes or syringe needles of different gauges. A typical radius of each of the above macrocapsules was 2 cm. To make capsules containing particles, 0.25–0.5% CB or 0.1% of GFPL were added to the biopolymer feed solution. This was then sonicated using a tip sonicator for 1 min to disperse the particles prior to its use for capsule synthesis.

In addition to the above capsules, all of which are electroresponsive (Figure S1, Supporting Information), two other particles were studied as non-responsive controls. Spherical agarose gels were made by dissolving 2% agarose in DI water at 90 °C and then adding this hot solution into spherical molds (5 mm radius), followed by cooling to room temperature. Also, chitosan-GA capsules were made in a manner similar to the chitosan-SDBS ones above, with 2% chitosan dropped into a mixture of 1% TPP and 2% GA and incubated for 15 min.

Microcapsule Synthesis: Microcapsules (sizes < 1 mm) were prepared using a microfluidic method developed by our group that has been described in detail previously.[8] The feed and reservoir solutions for each type of capsule were identical to those mentioned above. The feed flow was controlled by a syringe pump and the feed was sent through a glass capillary tube with an inner diameter typically of 200 µm. Compressed nitrogen gas was sent as a sheath around the capillary. A gas-flow controller was connected to a function generator (BK Precision) to generate gas pulses, with the gas pressure set at 14 psi. Details of the setup, together with photos, are provided in the SI section of our earlier paper.[8] For every pulse of gas, an aqueous droplet was dislodged from the tip of the capillary. The flow rate of the liquid as well as the frequency of the pulsing gas dictated the volume of the liquid droplet. Droplets generated this way were very uniform, with polydispersities of < 3% in their size.[8] Upon incubation in the reservoir solution, the droplets were converted to microcapsules. Thereafter, they were filtered out, washed with DI water, and stored in a 10 mM NaCl solution.

Electrical Rupture Tests: Figure 2 shows a schematic and photo of the test cell. It consists of a transparent cubical box (≈2 × 2 × 2 cm) made from plastic, with two planar graphite electrodes fixed vertically in the box on either end and separated by 1.7 cm. The test cell was filled with 3 mL of solution, which was typically 10 mM NaCl. A DC power source (Agilent E3612A) was connected to the two electrodes and a bias of 15 V was applied across the test cell. For monitoring the response of microcapsules, the box was placed on an inverted microscope for observation.

Optical and Fluorescence Microscopy: Brightfield images of the microcapsules under the field were obtained using an inverted optical microscope (Zeiss Axiovert 135 TV) using a 2.5× objective. Fluorescence images of capsules containing GFPL particles were taken using a band pass excitation filter (450-490 nm) and a band pass emission filter (515-565 nm). All images were analyzed using ImageJ software.

Ca^{2+}-EBT Colorimetry: The EBT solution was made by dissolving 0.005 g EBT in 20 g DI water. The ammonia buffer was prepared by mixing 2 mL of 29% ammonium hydroxide, 1 mL of concentrated HCl, and 2 mL of DI water. Alginate-Ca^{2+} macrocapsules were made as described above with their incubation time extended to 24 h so that they did not break in the field. For each experiment, 5 capsules were placed in the test cell along with 2 mL of 10 mM NaCl (see schematic in Figure S3B, Supporting Information). A given voltage (0, 6, 7, or 15 V) was then applied for 10 min. Next, 1 mL of the solution in the test cell (around the capsules) was quickly withdrawn using a micropipette and mixed with 150 µL EBT solution and 150 µL ammonia buffer. The color of this solution was then noted. For comparison, standard solutions with different Ca^{2+} concentrations (0 to 0.1% Ca^{2+} in 0.005% increments) were prepared by combining weighed amounts of $CaCl_2$•$2H_2O$ with 150 µL EBT solution and 150 µL ammonia buffer. The results are shown in Figure S3 (Supporting Information).

Statistics: Values of the capsule breaking time shown in Figure 6 and Figure S2 (Supporting Information) were determined from videos of electrical rupture tests and used without any transformation or normalization. At least three samples were tested for each data point. No outliers were excluded. Mean values are shown in the plots and error bars correspond to standard deviations. Statistics were calculated and plotted using Excel and SigmaPlot.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

alginates, electrically actuated valves, electrically induced drug deliveries, electroresponses, smart capsules

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