

Alginate–Polyethylene Oxide Blend Nanofibers and the Role of the Carrier Polymer in Electrospinning

Carl D. Saquing,^{†,||} Christina Tang,^{†,§} Brinda Monian,[†] Christopher A. Bonino,[†] Joshua L. Manasco,[†] Eben Alsberg,[‡] and Saad A. Khan^{*,†}

[†]Department of Chemical and Biomolecular Engineering, North Carolina State University, Raleigh, North Carolina 27695-7905, United States

[‡]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio 44106-7207, United States

Supporting Information

ABSTRACT: We present here a systematic investigation to understand why aqueous sodium alginate can only be electrospun into fibers through a blend with another polymer; specifically, polyethylene oxide (PEO). We seek to examine and understand the role of PEO as the “carrier polymer”. The addition of PEO favorably reduces electrical conductivity and surface tension of the alginate solution, aiding in fiber formation. While PEO has the ability to coordinate through its ether group ($-\text{COC}-$) with metal cation like the sodium cation of sodium alginate, we demonstrate in this study using PEO as well as polyvinyl alcohol (PVA) that coordination may have little effect on electrospinnability. More importantly, we show that PEO as carrier polymer provides molecular entanglement that is required for electrospinning. Since the selected carrier polymer provides the necessary entanglement, this carrier polymer must be electrospinnable, entangled and of a high molecular weight (more than 600 kDa for PEO). On the basis of these requirements, we stipulate that the PEO–PEO interaction of the high molecular-weight entangled PEO is key to “carrying” the alginate from solution to fibers during electrospinning. Further, using the resulting understanding of the role of PEO, we were able to increase the alginate concentration by employing a higher molecular-weight PEO: up to 70 wt % alginate using 2000 kDa PEO and, with, the addition of Triton X-100 surfactant, up to 85 wt % alginate, higher than previously reported.

INTRODUCTION

In the past decade, electrospinning has attracted great attention due to an increased interest in nanoscale properties and technologies.^{1–3} This technique has become a versatile and valuable route in the production of exceptionally long polymer fibers with uniform diameters ranging from 10 nm to greater than 10 μm .^{4,5} In electrospinning, typically, a polymer solution or melt is extruded through a capillary tube (spinneret) to form a small droplet at the spinneret tip. The application of voltage between the tip of the spinneret and the collection plate generates surface charges in the polymer droplet, and when the applied voltage is above a critical value, the electrostatic forces overcome the surface tension in the polymer drop causing it to stretch to form a cone (referred to as a Taylor cone) and eventually a liquid jet that is accelerated toward the grounded collection plate. During the flight of the resulting polymer jet, it experiences a combination of stretching and whipping (accompanied by solvent evaporation of polymer solutions) leading to continuous ultrathin randomly oriented fibers in the form of a nonwoven mat. It is generally recognized that solution viscosity, surface tension, and electrical conductivity, among other parameters, greatly influence fiber formation (bead-free) and diameter.⁶ Higher viscosity and conductivity and lower surface tension tend to yield bead-free fibers, although extreme values can lead to practical difficulties in electrospinning.⁷

Although electrospun nanofibrous polymers are widely recognized to have potential applications in filtration, catalysis, and sensing,⁸ they may also be useful in a wide variety of

biomedical applications.^{9–11} In particular, polymer nanofibers can serve as tissue scaffolds, providing mechanical support for cellular activities and growth,^{12–14} because they resemble the body’s natural extracellular matrix (ECM).¹⁵ Previous studies show that scaffolds with nanoscale features better support cell attachment and proliferation when compared to scaffolds with micrometer size structures due to increased cellular attachment.^{9,16–20} Furthermore, electrospun nanofiber membranes have excellent porosity, which is essential to allow for better cell adhesion, cell ingrowth, and nutrient exchange during *in vivo* or *in vitro* cell culture.^{15,21}

Nanofibers made of natural polymers may be particularly well-suited for tissue engineering applications because natural polymers are biocompatible and biodegradable.^{21–23} They are known to induce an appropriate response in a host organism, have resorbable biodegradation products, and often have reduced toxicity and inflammatory and immune responses.^{24–26}

Commonly used natural polymers in tissue engineering are collagen, gelatin, hyaluronan, chitosan, gelatin, and alginate.^{27,28} Recently, collagen, chitosan, and alginate based nanofibers were successfully fabricated and showed good cellular compatibility.^{9,29–34} Additionally, composite nanofibers of silk fibrin and

Special Issue: Giulio Sarti Festschrift

Received: September 4, 2012

Revised: March 4, 2013

Accepted: March 4, 2013

Published: March 4, 2013



polyethylene oxide (PEO) have been fabricated and were able to support bone marrow stromal cell attachment and growth, despite the presence of the carrier polymer.^{35,36}

Alginate, a naturally abundant linear anionic polysaccharide extracted from brown sea algae, is of particular interest for tissue scaffolds, because it has a similar structure to one of the major components of the ECM in human tissue, glycosaminoglycan (GAG).^{37–40} It has been widely investigated for tissue engineering applications including cardiac tissue,⁴¹ bone,⁴² skin,⁴³ liver,⁴⁴ and cartilage⁴⁵ regeneration. However, alginate in aqueous solution does not readily electrospin. Typically, the addition of an electrospinnable polymer such as polyethylene oxide (PEO) or polyvinyl alcohol (PVA), similar to several other natural polymers, is required.^{9,24,46–50} One of the drawbacks in adding a second polymer to aid electrospinning is that the alginate content has been limited to 40 wt %.^{46,50,51}

Some studies have attempted to electrospin alginate by adding a strong polar cosolvent like glycerol and obtained nonbeaded fibers.⁵² With the addition of glycerol, the viscosity increased substantially while the solution surface tension and electrical conductivity decreased. The presence of the glycerol is thought to enhance alginate chain entanglements in solution as indicated by changes in solution rheology, which presumably led to production of fibers. Alternatively, Bhattacharai et al. increased the alginate content to 80 wt % by adding 5 wt % dimethylsulfoxide (DMSO), an organic solvent, and 0.5 wt % Triton X-100, a nonionic surfactant, to the alginate-PEO.⁹ They surmised that a dipole–dipole interaction was introduced between alginate chains and DMSO since DMSO has a large dipole.

Although seemingly intuitive, a fundamental understanding of how electrospinning is facilitated in alginates has yet to be established. Several conjectures regarding successful fiber formation have been made, including sufficient alginate entanglement, electrospinnability of the carrier polymer, and interactions between alginate and carrier/cosolvent. The use of surfactants to screen charges has also been suggested to further improve the electrospinnability of alginates. In this work, we focus on a systematic understanding of the role of the carrier polymer and surfactant in relation to alginate electrospinning, particularly with respect to the effect on polymer chain dynamics in solution.

It has been shown empirically that fiber formation during electrospinning^{54,55} is strongly correlated with the amount of polymer chain entanglements in solution (C/C_e , where C is the polymer concentration and C_e is the chain entanglement concentration) for both neutral⁵⁵ and polyelectrolyte⁵⁶ polymers. Further, viscosity scaling relationships can be used as a measure of chain entanglement. Colby et al. measured the concentration dependence of viscosity of linear polymers in good solvents and identified four different concentration regimes including the dilute, semidilute unentangled, semidilute entangled, and concentrated regimes.^{57,58} Boundaries between concentration regimes were identified: the chain overlap concentration (C^*) is the intersection between the dilute and semidilute unentangled regimes; the entanglement concentration, C_e , is the intersection of the semidilute unentangled and semidilute entangled regimes and is characterized as the stage at which significant overlap of the polymer chains topologically constrains the macromolecular chain motion, and C^{**} as the onset of the concentrated regime.⁵⁹ For neutral copolymers with molecular weights well above the entanglement molecular weight, C_e was the minimum concentration required for

electrospinning of beaded fibers, while 2–2.5 times C_e was the minimum concentration required for electrospinning of uniform, bead-free fibers.⁵⁵ On the other hand, for a cationic polyelectrolyte solutions of poly(2-(dimethylamino)ethyl methacrylate hydrochloride) (PDMAEMA-HCl), fiber formation was achieved at concentrations of at least 8 times C_e .⁵⁶

Utilizing viscosity scaling relationships to obtain a measure of polymer entanglement, we aim to better understand the role of additives (carrier polymers, cosolvents, and surfactants) to the system.^{60–68} In this study, alginate blended with PEO in aqueous solution was electrospun, sometimes with the addition of a model nonionic surfactant Triton X-100, to thoroughly characterize the effect of this surfactant on the system and maximize the alginate content without the addition of an organic solvent. We also systematically investigated the onset of chain entanglement in aqueous alginate solutions both in the absence and presence of PEO with varying molecular weights (100, 200, 600, 1000, and 2000 kDa) in order to determine the role of carrier polymer chain entanglement in fiber formation. Changes in solution properties such as electrical conductivity, shear viscosity, and surface tension were also determined to further understand the relationship between the electrospinnability of the system and solution properties. Additionally, polyvinyl alcohol (PVA) and PEO both have been shown by experiment and ab initio calculations to have the ability to coordinate with metal cations; hence, here we consider coordination between the carrier polymer and sodium cation in sodium alginate when in solution which may also affect electrospinnability.^{69,70} We demonstrate that a successful carrier polymer, which is one that facilitates production of bead-free high alginate content fibers (up to 85 wt %), must not only be electrospinnable, but must also have a high molecular weight. We stipulate that at sufficiently large molecular weights, the carrier polymer entangles despite the presence of alginates and it is these carrier polymer (e.g., PEO-PEO) interactions that facilitate electrospinning.

We would like to reiterate that the focus of this study has been on the carrier polymer and explaining its role in terms of entanglement and viscosity. We make no attempt to decipher the mechanism of fiber formation in the electrospinning process. Some elegant work has been done in this regard to show that small molecules without entanglements can be electrospun, that relaxation time, viscoelasticity and extensional rheology play a critical role in fiber formation, and correlation can be derived between fiber diameter and solution properties.^{71–78} These are important issues, but they fall outside the realm of this study, both from its scope and length.

■ EXPERIMENTAL SECTION

1. Solution Preparation. For a typical procedure, predetermined amounts of alginate (Sigma, Viscosity (25 °C, 2 wt % aqueous solution) = 250 or 2000 cP, low viscosity or medium viscosity, with corresponding average molecular weights of 46 and 100 kDa, respectively), PEO (Polysciences, MW = 100–2000 kDa) and Triton X-100 (Sigma, Ultrapure) were dissolved in deionized water. Unless otherwise indicated, the standard molecular weight of PEO used was 1000 kDa. The alginate and PEO aqueous mixtures were stirred for 3–4 h to ensure complete dissolution, after which the two solutions were combined in certain ratios and stirred several more hours. Subsequently, the surfactant was added and the mixture was stirred overnight. In another set of experiments, instead of surfactant, salt (sodium chloride, Sigma) was added to

determine the effect of drastic increase in electrical conductivity to electrospinning aqueous alginate–PEO solutions. After the dissolution, the resulting solution was left for half an hour to eliminate any air bubbles and was subsequently electrospun or analyzed further. All concentrations are in weight percent unless otherwise stated.

2. Solution Characterization. Rheological analysis was performed at 25 °C using a TA Instruments AR-G2 stress-controlled rheometer fitted with a 40 mm, 2° cone and plate geometry. Steady shear experiments were performed on each sample. To ensure uniform solution conditioning, a preshear was applied at a shear stress of 1 Pa for 60 s followed by a rest period of 120 s. Zero-shear viscosity was determined from the steady shear experiments. It is to be noted that shear viscosity is being used here as a proxy for extensional viscosity, which would be important in electrospinning but difficult to measure. Each experiment was performed at least twice, which were reproducible within ± 5 wt %. Surface tension was measured using a Wilhelmy plate (Sigma 70, KSV Instruments Ltd.),⁶⁰ and solution conductivity was measured with a conductivity meter (Fisher Accumet BASIC AB30) as described previously.⁶¹

3. Electrospinning. The design of the electrospinning setup was based on a point-plate configuration, using a precision syringe pump (Harvard Apparatus, Holliston, MA) and a high-voltage power supply (Gamma High Voltage Research, model D-ES30 PN/M692). Details of the apparatus have been previously described.⁶¹ Typically, a flow rate of 0.5 mL/h, a tip to collector distance of 15 cm, and a voltage of 6–12 kV was used. The morphology and size of the resulting electrospun nonwoven fiber mats were evaluated using scanning electron microscopy (SEM, FEI XL30).

RESULTS AND DISCUSSION

1. Electropinnability of Aqueous Sodium Alginate.

Previous studies have shown that aqueous solutions of sodium

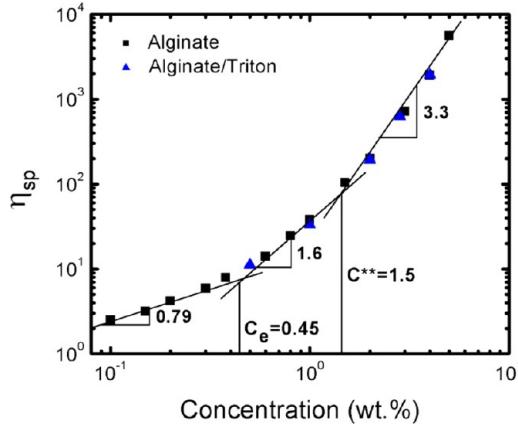


Figure 1. Specific viscosity (η_{sp}) concentration dependence for low-viscosity alginate (black squares) and alginate-1 wt % Triton (blue triangles) systems in water showing polyelectrolyte solution dynamics.

alginate do not form fibers through electrospinning.^{9,50} Nie et al. suggested that the rigid and extended worm-like molecular chains of alginate prevent chain entanglement in aqueous solution, thus inhibiting fiber formation during electrospinning.⁴⁹ We began by identifying the entanglement concentration for alginate and attempting to electrospin concentrations up to saturation, since we hypothesize that

Table 1. Solution Properties of Alginate, Alginate/PEO, and Alginate/PEO/Triton Systems in Water at Room Temperature As It Relates to Electrospinning

solution composition	electrical conductivity (mS/cm)	surface tension (mN/m)	viscosity (Pa·s)	fiber formation
without Triton				
4 wt % alginate	8.8 ± 0.1	60.9 ± 1.7	1.9 ± 0.1	no
4 wt % Alg/PEO (70/30)	5.8 ± 0.1	50.7 ± 1.1	4.6 ± 0.2	no
4 wt % Alg/PEO (50/50)	4.0 ± 0.1	45.8 ± 1.0	5.5 ± 0.3	yes
4 wt % Alg/PEO (30/70)	2.4 ± 0.1	41.1 ± 1.8	9.3 ± 0.5	yes
4 wt % PEO	0.07 ± 0.1	36.8 ± 2.1	14.7 ± 0.7	yes
with Triton (1 wt %)				
4 wt % alginate	8.6 ± 0.1	26.1 ± 1.1	1.8 ± 0.1	no
4 wt % Alg/PEO (70/30)	5.8 ± 0.1	22.6 ± 1.4	4.5 ± 0.2	yes
4 wt % Alg/PEO (50/50)	4.0 ± 0.1	21.5 ± 1.3	5.6 ± 0.3	yes
4 wt % Alg/PEO (30/70)	2.3 ± 0.1	17.8 ± 1.0	9.2 ± 0.5	yes
4 wt % PEO	0.08 ± 0.1	13.7 ± 0.8	14.6 ± 0.7	yes

concentrations previously used in some studies may not have been sufficiently above the entanglement molecular weight to allow for fiber formation.

By measuring the specific viscosity (η_{sp}) as a function of polymer concentration, we established the semidilute unentangled and semidilute entangled regimes (Figure 1).^{55,58} The viscosity scaling relationships obtained for alginate were $\eta_{sp} \sim C^{0.79}$ for the semidilute unentangled region, $\eta_{sp} \sim C^{1.6}$ for the semidilute entangled region, and $\eta_{sp} \sim C^{3.3}$ for the concentrated region, which agrees well with the theoretical predictions for polyelectrolyte systems which are $\eta_{sp} \sim C^{0.5}$, $\eta_{sp} \sim C^{1.6}$, and $\eta_{sp} \sim C^{3.6}$, respectively,⁶² thus reinforcing the polyelectrolyte behavior of alginate in water and is similar to previous studies of cationic polymers.⁶³ Interestingly, the scaling relationship in the concentrated regime for the alginate system approximates that of the neutral polymer because the electrostatic charges are screened with the overlap of the electrostatic droplets as theoretically predicted.⁶²

Also, based on these data, the entanglement concentration of aqueous alginate is 0.45 wt % alginate consistent with previous studies.^{49,50} According to McKee et al., fiber formation with polymer solution electrospinning is realized at a concentration of at least 2–2.5 times C_e for a neutral and nonassociating polymer and 9 times C_e for polyelectrolytes.^{56,63} Therefore, in the case of alginate, we may anticipate that at concentrations above 4 wt % fibers could be formed. However, we were not able to form fibers even at estimated saturation concentration of 6 wt % (13 C_e). SEM results for all alginate concentrations (1–6 wt %) tested (Supporting Information—Figure A) show that only large polymer droplets (no bead-free fibers or even beaded-fibers) were achieved at all concentrations. Therefore, results indicated that the inability to electrospin aqueous sodium alginate is not due solely to a lack of entanglement.

The large size of the droplets seemed to indicate that the high surface tension of alginate solution may prevent fiber formation, so the addition of surfactant was also tested. Bhattacharai et al. used Triton X-100, a nonionic surfactant to electrospin sodium alginate/PEO blend in H₂O/DMSO mixture and successfully electrospun fibers with 80 wt % alginate content.⁹ We explored the addition of Triton X-100 in

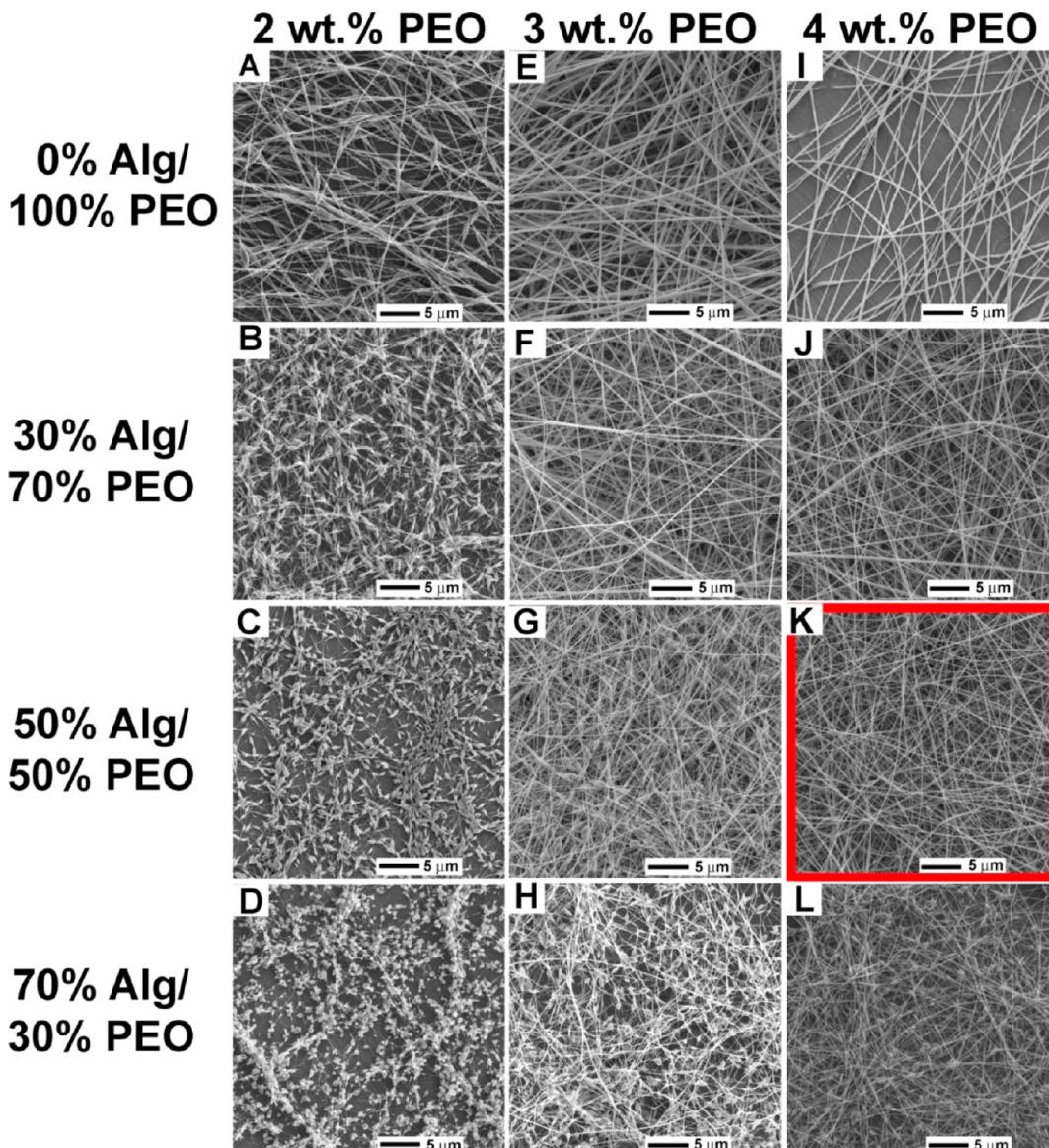


Figure 2. SEM images of electrospun fibers from low-viscosity alginate and PEO blends, combining 3 wt % alginate and various percents PEO in different ratios showing that the maximum alginate content (K, outlined in red) of bead-free fibers is about 43 wt %. Note that 43 wt % refers to the absolute percentage of alginate in the nanofibers after electrospinning and not the solution.

sodium alginate in water (without DMSO) to determine if and how the reduction of the surface tension would improve fiber formation. The concentration of Triton used ranged from 0.6 to 1.0 wt % (40–67 times the critical micelle concentration), and results from SEM analyses show that polymer droplets formed after electrospinning in all concentrations of alginate (3–6 wt %) used and no fiber formation were observed. However, the size of the droplets was reduced dramatically with the addition of 1 wt % Triton (representative results shown in Supporting Information Figure A). Examining the solution properties, we found that the addition of 1 wt % Triton in 4 wt % alginate reduced the surface tension by at least a factor of 2, without significantly changing the solution viscosity and electrical conductivity (Table 1). Further, we verified that the addition of Triton at a fixed concentration of 1 wt %, did not affect the polymer entanglement (Figure 1). This is consistent with the no-participation of Triton in the screening of the repulsive electrostatic charges (previously suggested for other polyelectrolytes) masking polyelectrolyte chain dynamics in

solution.⁵⁶ Because the droplets remained, the reduction of surface tension, though favorable to formation of fibers as indicated by the production of smaller droplets, is not the only factor in electrospinning alginate fibers. On the basis of the aforementioned results, we believe that the high electrical conductivity of the alginate solution coupled with high surface tension also inhibit fiber formation, despite the presence of chain entanglement.

2a. Electrosprining of Sodium Alginate–PEO Blends. It has been previously shown that blending alginate with an electrospinnable polymer (for example, PEO or PVA), enables the formation of nanofibers by electrospinning.^{9,46–50} However, very few studies comprehensively investigated the correlation of the addition of these carrier polymers on the resulting viscosity, electrical conductivity, and surface tension as well as the viscosity scaling relationships, a measure of chain entanglement, as they relate to electrospinnability.^{47,54,56,57} Hence, in the following experiments, we tried to decouple the effect of these parameters on the electrospinnability of alginate. We studied

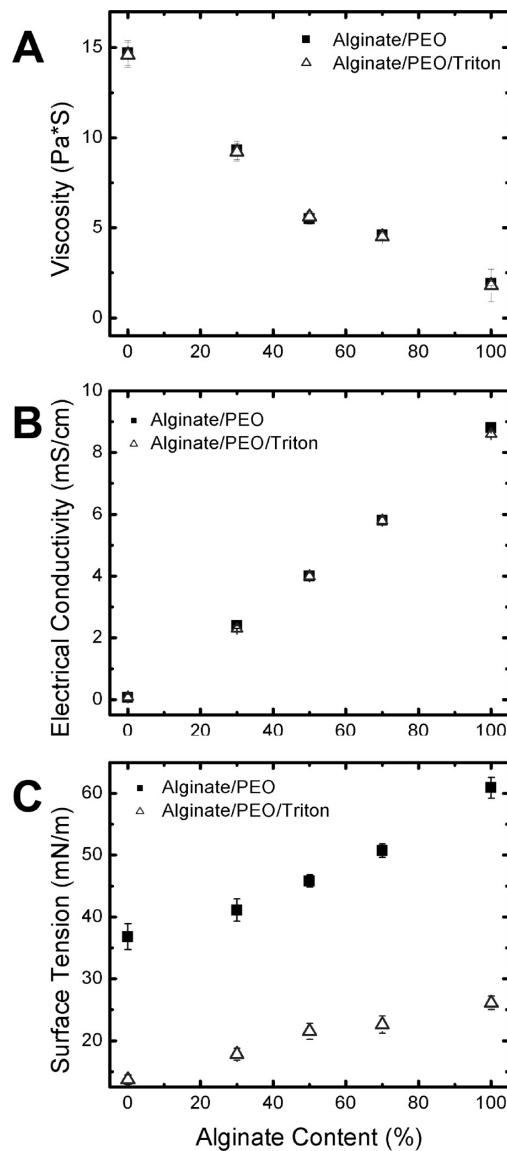


Figure 3. (A) Viscosity, (B) electrical conductivity, and (C) surface tension of aqueous low-viscosity alginate and PEO blends in the absence and presence of Triton. The total polymer concentration is fixed at 4 wt %.

the addition of PEO as an electrospinnable carrier polymer and examined the effect of adding Triton as a model surfactant and related the change of solution properties to electrospinnability and fiber formation.

Figure 2 shows the SEM images of the electrospun fibers after the addition of PEO (with MW = 1000 kDa) at different concentrations (2–4 wt %) in a fixed concentration of alginate (3 wt %) (Figure 2). When alginate is combined with 2 wt % PEO, fibers obtained at all alginate to PEO ratios were beaded (Figures 2A–D), and the degree of beading increases with increasing alginate content. However, when alginate is combined with PEO at concentrations of 3 and 4 wt %, nonbeaded fibers were obtained at alginate ratios of 30% (Figure 2F) and 50% (Figure 2K), respectively, which resulted in a maximum alginate content of 43 wt %, similar to previous reports.^{46,50} Note that 43 wt % corresponds to the absolute percentage of alginate in the nanofiber after electrospinning whereas 50% refer to percentage of alginate in the solution.

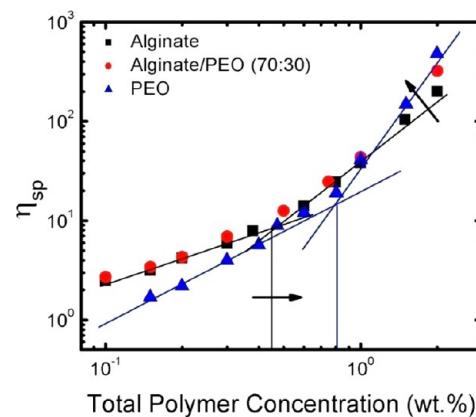


Figure 4. Comparison of the viscosity scaling relationships of alginate, alginate/PEO (70/30 wt. ratio), and PEO systems in water using low-viscosity alginate. With increasing PEO concentration, the apparent entanglement concentration increases and the scaling relationship in the semidilute entangled region increases as highlighted by the arrows, which indicated a shift in polymer solution dynamics of alginate toward a neutral polymer behavior.

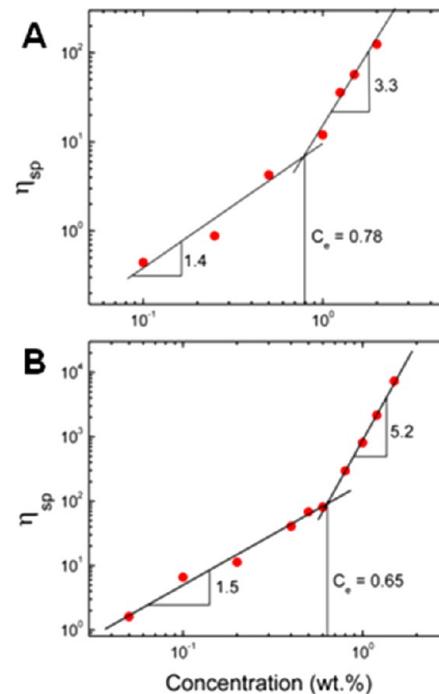


Figure 5. Comparison of the viscosity scaling relationships of alginate using the 1.5 wt % PEO viscosity as the solvent viscosity (A) and alginate using glycerol as a solvent (2:1 v:v ratio of glycerol to water) (B). In both cases, the entanglement concentration is higher than that of aqueous alginate. In the case of PEO, the scaling relationships approach that of a neutral polymer in a good solvent.

2b. Effect of PEO on Alginate Solution Properties. To understand the effect of PEO in electrospinning alginate, the viscosity, electrical conductivity, and surface tension were measured holding the total polymer concentration constant (4 wt %) and varying the ratio of PEO to alginate (Figure 3).

With increasing alginate concentration in the blends (reduced ability to form fibers), the viscosity decreases dramatically (Figure 3A), indicating that the addition of PEO aids electrospinnability in part by increasing the viscosity of the resulting solution. Dynamic data of elastic (G') and viscous

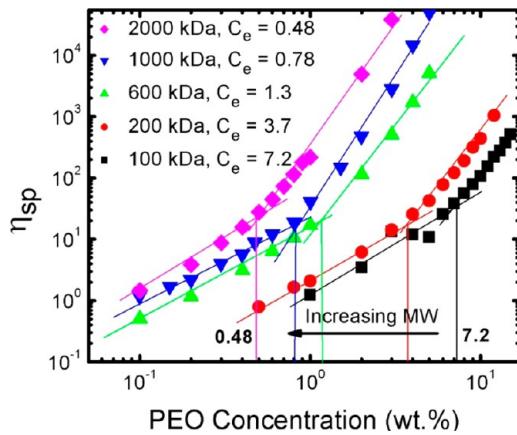


Figure 6. Specific viscosity (η_{sp}) dependence on concentration for PEO with different molecular weights ranging from 100 to 2000 kDa. The entanglement concentration, C_e , was determined from the η_{sp} dependence on concentration and is shown for each PEO.

(G'') moduli (Supporting Information Figure B) shows relaxation time also increases upon PEO addition. However, the solution electrical conductivity and surface tension are also affected by the addition of PEO, both decreasing with increasing PEO concentration. For instance, at a 40:60 alginate:PEO ratio where nonbeaded electrospun fibers can be achieved, the viscosity is increased by a factor of 2.5 times that of the alginate solution, and the electrical conductivity and surface tension are reduced from those of the alginate solution by almost 50% and 20%, respectively. The reductions in surface tension and conductivity, though slight compared to the increase in viscosity, also help facilitate fiber formation.⁵⁰ Since electrical conductivity, surface tension, and viscosity change with the addition of PEO, we attempt, in the next sets of experiments, to isolate the effect of each solution property on fiber formation, as well as to maximize the alginate content of the electrospun fibers.

2c. Effect of PEO on Alginate Rheology and Chain Entanglement. With the improvement of the electrospinnability of alginate through the addition of PEO, we were interested in evaluating the solution viscosity of the polymer blends. We examined the viscosity scaling relationships, varying the different ratios of alginate and PEO from 0% to 100% alginate content. We observed a shift in the C_e of the system from 0.45 for the pure alginate to 0.8 for neat PEO (Figure 4), with the alginate/PEO (70/30) blend somewhere between 0.5 and 0.6 indicating the influence of PEO in the overall solution behavior (pulling up the C_e of the system as the C_e of pure PEO is higher). More importantly, the viscosities differ most at higher concentration and the viscosity power-law behavior was found to be affected by the addition of PEO. For example, the viscosity scaling relationships obtained for alginate–PEO system (70:30 alginate:PEO ratio) were $\eta_{sp} \sim C^{0.85}$ for the semidilute unentangled region, $\eta_{sp} \sim C^{2.37}$ for the semidilute entangled region and $\eta_{sp} \sim C^{3.45}$ for the concentrated region. These results show that the addition of PEO to alginate solution (PEO replaced 30% of alginate) affected the η_{sp} only at the semidilute entangled regime as evident by the substantial change in the slope from 1.6 to 2.37 (theoretically predicted to be 3.75).⁶⁶ This change is a reflection of the effect of PEO shifting the solution dynamics toward a more neutral polymer solution behavior.

If we examine the solution rheology considering PEO to be part of the solvent system, i.e., calculate the specific viscosity using the PEO solution viscosity as the solvent viscosity, alginate behaves similarly to a neutral polymer in a good solvent (Figure 5A). The viscosity scaling relationships obtained in this case were $\eta_{sp} \sim C^{1.4}$ for the semidilute unentangled region (theoretical $\eta_{sp} \sim C^{1.25}$) and $\eta_{sp} \sim C^{3.3}$ for the semidilute entangled region (theoretical $\eta_{sp} \sim C^{3.75}$), with an entanglement concentration of 0.78 wt % alginate. This result indicates that in solution, the presence of PEO helps reduce alginate–alginate interactions so that PEO–PEO interactions dictate the solution behavior since polyelectrolytic behavior is no longer observed.

Since alginate in a mixture of glycerol and water as solvent has been reported to generate electrospun bead-free fibers, we did examine the rheological behavior of our alginate in a glycerol–water mixture to compare with PEO.⁵² When using glycerol as a cosolvent, the viscosity scaling relationships were $\eta_{sp} \sim C^{1.5}$ for the semidilute unentangled region and $\eta_{sp} \sim C^{5.2}$ for the semidilute entangled region (Figure 5B). There is an increase in the scaling relationship in the semidilute entangled region which may be an indication of increased molecular interactions as increased concentration dependence has been reported when salt is added to polyelectrolyte solutions and associating polymers.⁵³ However, the entanglement concentration when using glycerol is 0.65 wt % alginate, higher than alginate in water (0.45 wt %). On the basis of viscosity scaling relationship, it does not appear that the presence of glycerol increases alginate entanglement. This may explain why we were not able to reproduce electrospun bead-free alginate fibers from a mixture of glycerol and water.

2d. Effect of PEO Molecular Weight on Alginate Electrospinning. According to Nie et al., the ability of the PEO to influence the electrospinnability of alginate requires the presence of PEO chain entanglements.⁴⁹ At a molecular weight of 20 kDa, they determined that PEO did not form molecular entanglements at all concentrations (up to 35% (w/v)) and, thus, explained why no bead-free fibers were formed when blended with alginate. We expanded on their work, using PEO with molecular weights between 100 and 2000 kDa. We found entanglement concentrations for 100, 200, 600, 1000, and 2000 kDa using the specific viscosity dependence on concentration for each of the molecular weights, and these results are shown in Figure 6. The C_e were estimated to be 7.2, 3.7, 1.3, 0.78, and 0.48 wt % for 100, 200, 600, 1000, and 2000 kDa, respectively.

Aqueous PEO with initial concentrations of 15 (100 kDa), 7 (200 kDa), 5 (600 kDa), 3 (1000 kDa), and 3 (2000 kDa) wt % was mixed with aqueous alginate (with initial concentration fixed at 3 wt %) at weight ratios of 30:70, 50:50, and 70:30 (alginate:PEO) and electrospun. The choice for the initial concentration of each PEO was made using two criteria: (1) that the resulting alginate–PEO solution blends have similar viscosity and (2) that the blend approximates at least $2.5C_e$. However, due to solubility issues, the initial concentration of 100 and 200 kDa were limited to 15 and 7 wt % which is close to $2.0C_e$. Figure 7 shows SEM images after electrospinning the alginate–PEO solutions.

Blends with entangled 100 and 200 kDa PEO did not produce defect-free fibers even if the absolute concentration of alginate with respect to PEO was as low as 8 wt %. We did not attempt to match other solution parameters (namely electrical conductivity and surface tension) with the various molecular weights; however, the variation in these parameters for lower

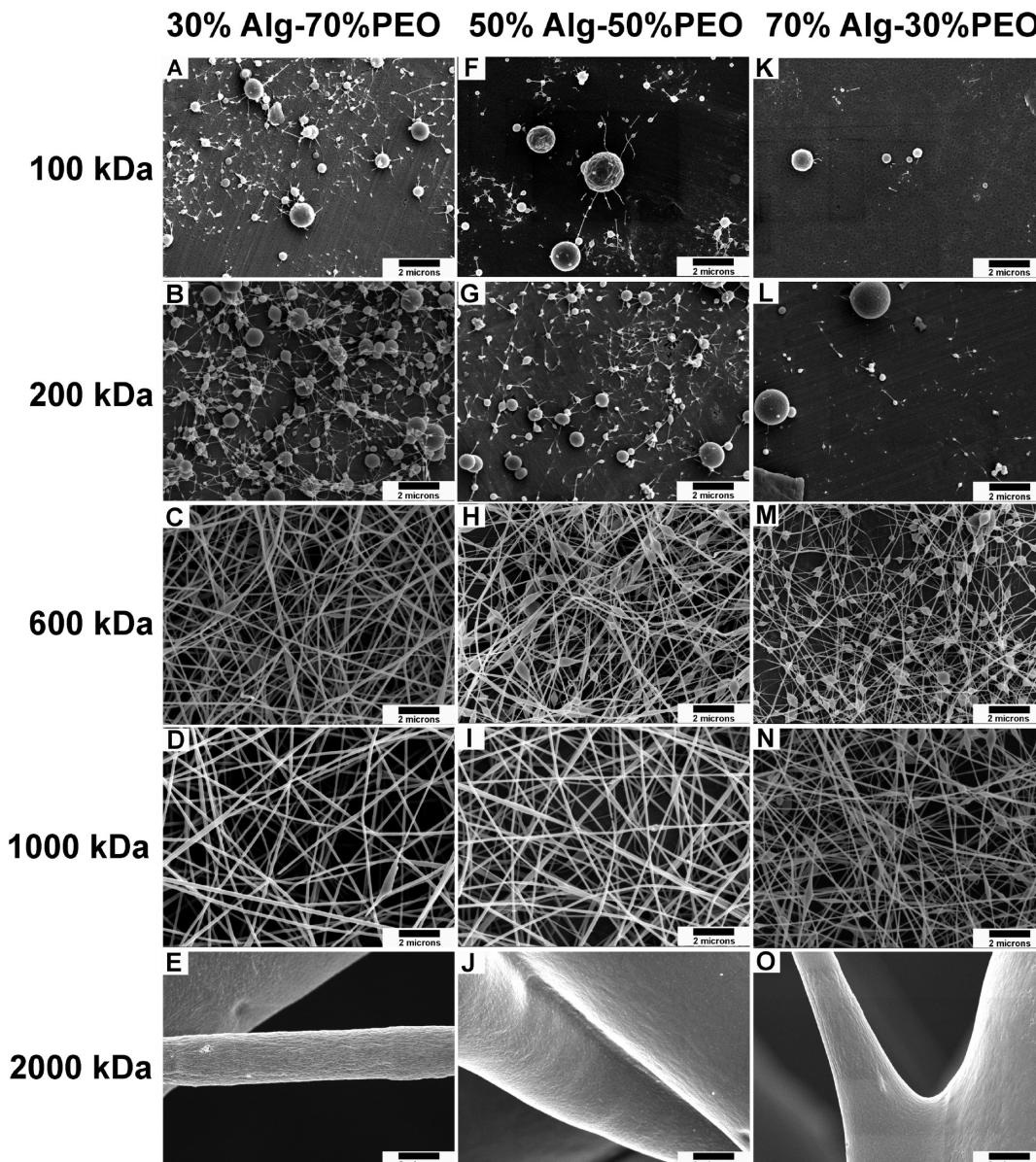


Figure 7. Effect of PEO molecular weight (100–2000 kDa) on electrospinning medium-viscosity alginate–PEO blends at weight ratios of 30/70 (A–E), 50/50 (F–J), and 70/30 (K–O). The concentration of alginate solution before mixing was fixed at 3 wt % while the concentrations of 100, 200, 600, 1000, and 2000 kDa PEO were 15, 7, 5, 3, and 1 wt %, respectively. The scale bar shown on each SEM micrograph is 2 μ m.

molecular weight PEO should be favorable to electrospinning since the absolute concentration of PEO in the alginate–PEO solution increases with decreasing PEO molecular weight.

To further understand why entangled 100 and 200 kDa PEO do not aid in fiber formation, we electrospun aqueous solutions of each molecular weight PEO by itself. Results show that even at concentrations approximating $2.5C_e$, bead-free nanofibers cannot be achieved (Supporting Information—Figure C) for these two molecular weights. These data demonstrate that carrier polymer entanglement does not guarantee the generation of bead-free electrospun fibers. A higher degree of molecular entanglements with the added polymer is required to elicit sufficient chain entanglements in the resulting polymer blend solution that would trigger fiber formation as seen for PEO with molecular weight ranging from 600 to 2000 kDa.

Interestingly, the alginate content of bead-free fibers increased with increasing PEO molecular weight. A maximum

of 70 wt % alginate content was achieved for 2000 kDa PEO (see Figures 7E, J, and O); however, the fiber diameter dramatically increased due to increased viscosity at this concentration. When we decreased the concentration for this system (alginate + PEO with MW = 2000 kDa) from 3 to 2 wt %, we were able to achieve bead-free fibers with submicrometer diameter (Supporting Information—Figure E) in all alginate–PEO ratios up to 70 wt % alginate content. However, if the PEO concentration was below the entanglement concentration, defect-free fibers were not obtained.

To further investigate the effect of carrier polymer entanglement, we extended our study to PVA, molecular weight 205 kDa, which has been previously electrospun.⁶⁸ On the basis of the entanglement molecular weight previously reported, we blended medium-viscosity sodium alginate with 7 wt % PVA at various ratios (Figure 8).⁶⁸ However, we were not

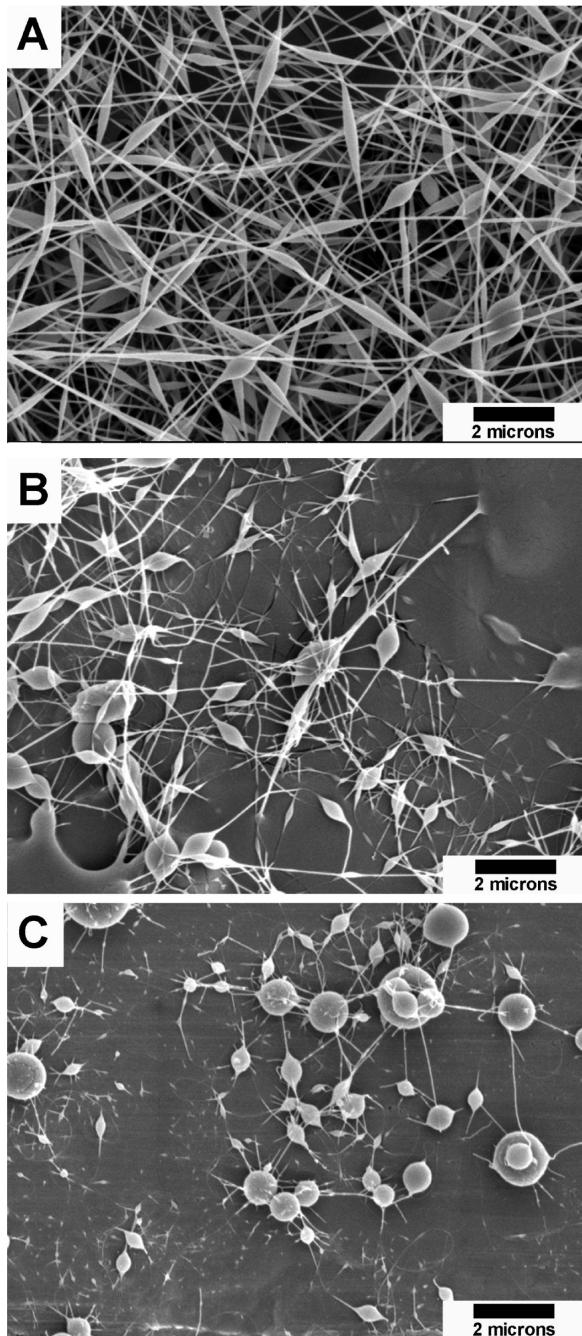


Figure 8. Effect of adding 205 kDa PVA (7 wt %) on alginate (3 wt %, medium viscosity) in (A) 30:70, (B) 50:50, and (C) 70:30 weight ratios.

able to produce uniform fibers, despite the fact that PVA on its own produces bead-free fibers.

This result further demonstrates that even if the electrospinnable carrier polymer has sufficient entanglement to form fibers on its own, it does not guarantee the generation of bead-free composite fibers when blended with alginate.

Using PVA in comparison with PEO, we also consider the effect of coordination between the sodium cation and the carrier polymer. Both PVA and PEO have the ability to coordinate with metal cations such as the sodium cation in sodium alginate. It has been demonstrated both by experiment and ab initio calculations that PVA coordinates through the hydroxyl group ($-\text{OH}$), whereas PEO coordinates through the

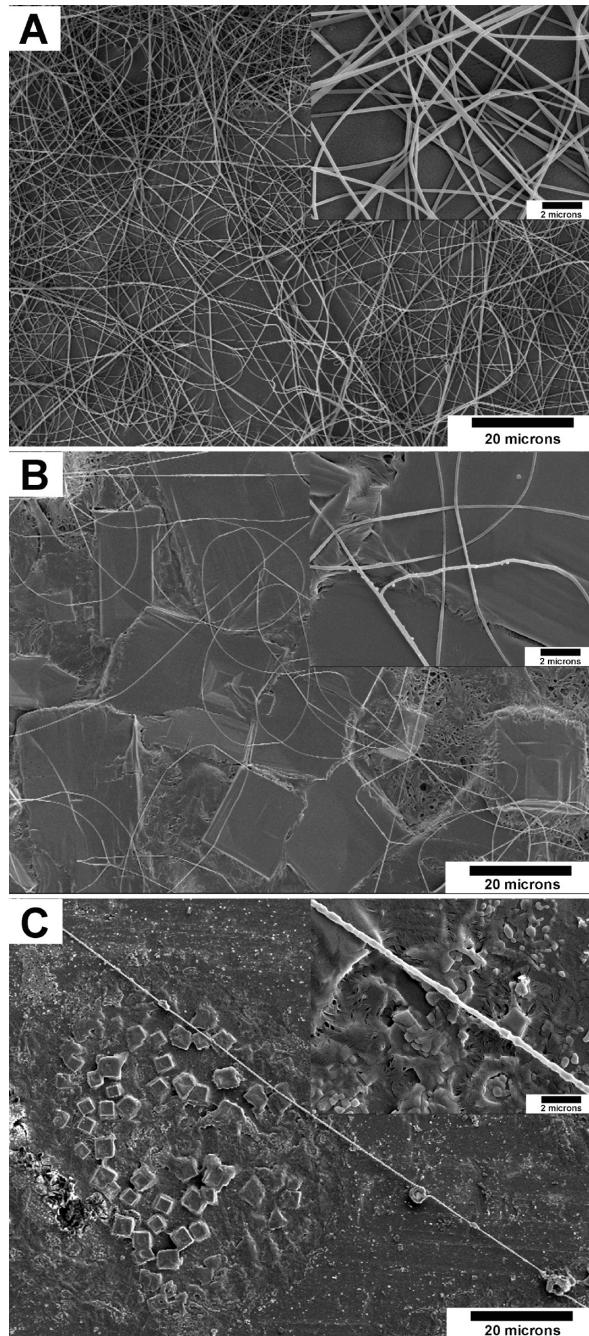


Figure 9. Effect of salt in (A) 0, (B) 1, and (C) 5 wt % concentrations on the electrosprinnability of a medium-viscosity alginate and PEO blended system. The total concentration of the polymer blend was fixed at 3 wt % at a 50:50 alginate to PEO ratio. Higher magnification SEM micrographs are shown as inserts with $2 \mu\text{m}$ scale bars.

oxygen of the ether group ($-\text{COC}-$), and the coordination through the hydroxyl group is stronger than through that of the oxygen of the ether group in PEO.^{69,70} Previously, we and others have shown that the increase in PEO MW increases the strength of metal coordination through the ether oxygen in PEO by virtue of the increased number of pseudocrown ethers (that can bind metal cations) formed in solution.^{61,79} Hence, since the electrosprinnability of alginate is affected by higher MW PEO as discussed earlier, we thought it expedient that another experiment to approximate the effect of metal coordination be attempted, thus the use of PVA.

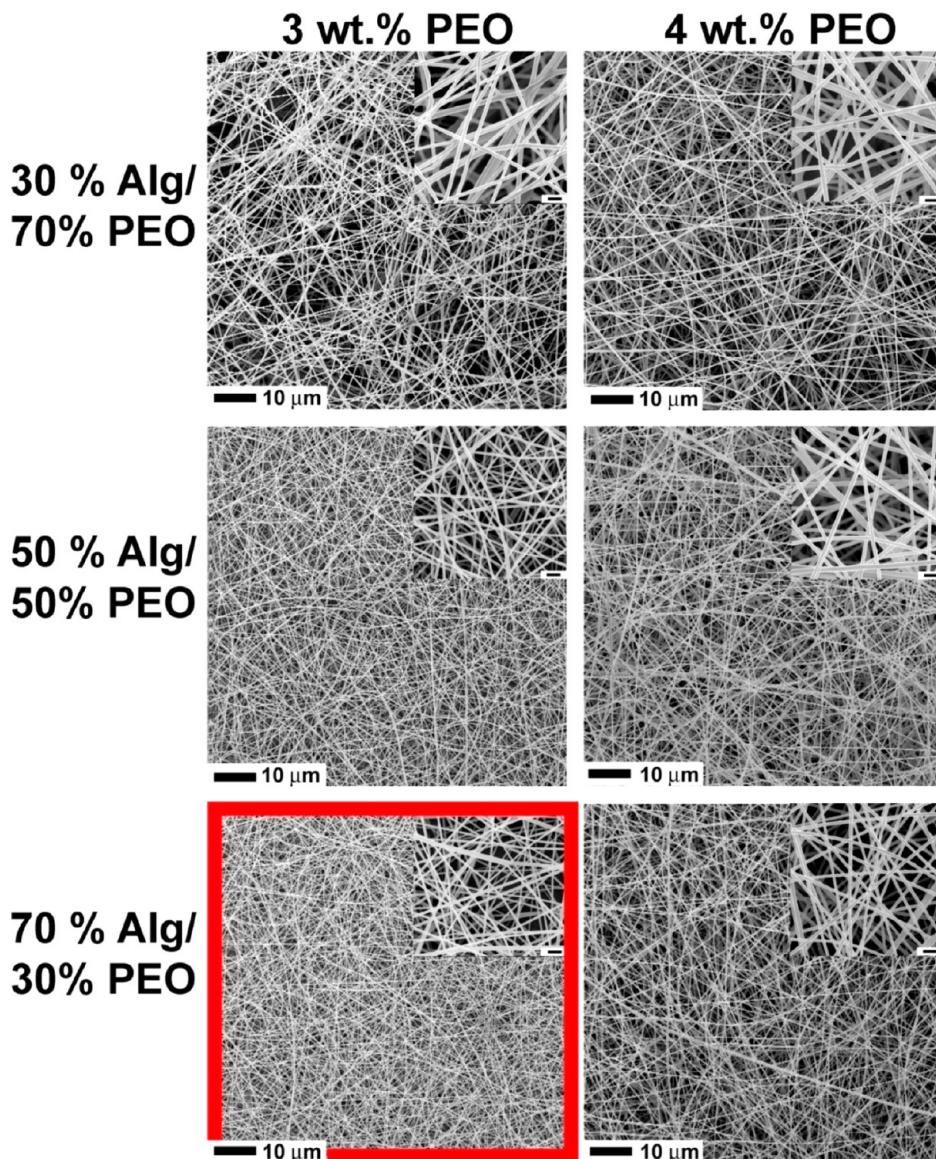


Figure 10. SEM images of electrospun fibers from low-viscosity alginate and PEO blends in various ratios with 1 wt % Triton, showing that the maximum alginate content can be increased to 70 wt % (outlined in red). (inset) Higher magnification SEM micrographs with a 1 μm scale bar.

Despite the increased strength of coordination in the case of PVA, we were still unable to obtain uniform blend fibers with alginate, although at the 30:70 alginate–polymer carrier ratio, we were able to obtain beaded fibers for the case of PVA (205 kDa) as carrier compared to mostly droplets for the case of PEO (200 kDa) as carrier, which may be due to the slightly higher viscosity of PVA. On the basis of these results, we infer that the electrospinnability of the blends cannot be significantly attributed to coordination of the carrier polymer and metal cations.

Through our systematic investigation with various molecular weights of PEO and comparison of PEO to PVA, we deduce that high molecular weight carrier polymers are required to produce sufficient chain entanglements in the resulting polymer blend solution to facilitate fiber formation as seen with higher molecular weight PEOs. These results suggest that the entanglements between the high molecular weight carrier polymer molecules, and not those between the carrier polymer and alginate, dominate the blend system, facilitating the electrospinnability of the solution.

3. Effect of Salt in a PEO–Alginate System. To confirm the effect of electrical conductivity on fiber formation, we examined the addition of salt to an electrospinnable alginate–PEO system. Previously, we have found that the presence of AgNO_3 and Ag nanoparticles improved the electrospinnability of PEO up to a certain Ag salt concentration, but further increase in Ag salt concentration disrupted fiber formation due to increases in solution electrical conductivity.⁶¹ In this experiment, we added salt to an electrospinnable aqueous alginate–PEO blend (50:50 alginate:1000 kDa PEO) (Figure 9A). The advantage of this approach is that the addition of salt (in this case NaCl) up to 5 wt % in aqueous alginate solution increased the electrical conductivity without altering the solution viscosity and surface tension. With the addition of NaCl, the electroconductivity increased from 2.21 (0 wt % NaCl) to 58.53 mS/cm (5 wt % NaCl). The presence of the NaCl, even at 1% in which no crystals are formed, disrupted fiber formation (Figure 9) validating our initial hypothesis that the high electrical conductivity of alginate has a substantial contribution to its inability to form fibers. Therefore, we

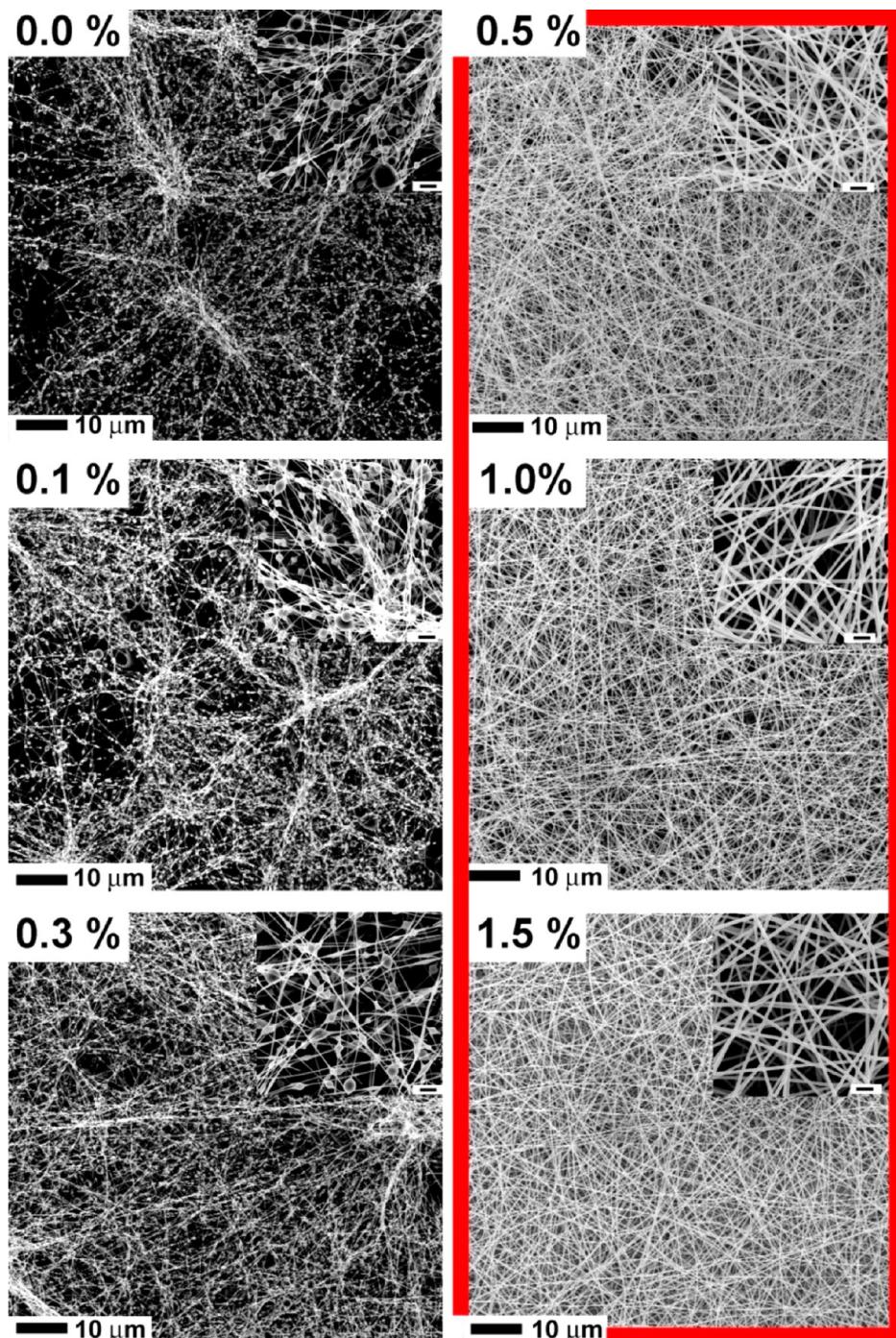


Figure 11. SEM images of electrospun fibers from a medium-viscosity alginate and PEO blend (fixed at 80/20 alginate-to-PEO ratio) at different Triton concentrations (given in weight percent). Bead-free fibers can be achieved with the addition of 0.5 to 1.5 wt % Triton. A maximum alginate content of 80 wt % was obtained (outlined in red). (inset) Higher magnification SEM micrographs with a 1 μm scale bar.

surmise that the addition of PEO improves electropinnability by reducing electrical conductivity.

4. Effect of Nonionic Surfactant in a PEO–Alginate System. Finally, we used a model nonionic surfactant (Triton X-100) to vary the surface tension of alginate/PEO blends. We note that addition of Triton (1 wt %) have minimal effect on the solution dynamics of the alginate–PEO blends (Supporting Information—Figure F). We hypothesized that decreasing the surface tension with the addition of a surfactant may compensate for the increase in electrical conductivity and

decrease in viscosity with increased alginate concentration and afford the production of higher alginate content fibers.

We were able to electrospin nonbeaded nanofibers with alginate content of at least 70 wt % by adding about 1 wt % Triton (Figure 10). Further, we explored increasing alginate content holding the surfactant concentration fixed at 1 wt %, and we achieved a maximum of 85% alginate (Supporting Information—Figure G).

We also explored the effect of surfactant concentration on fiber formation. Above the critical micelle concentration, surface tension is relatively independent of surfactant

concentration.⁸⁰ If the formation of fibers at higher alginate concentration is due in part to high surface tension, then we hypothesized that we should form fibers with the addition of surfactant as long as the surfactant concentration is above the CMC. Fixing the alginate:PEO ratio to 80:20, Figure 11 shows that fibers can be obtained at Triton concentrations of at least 0.5 wt % (33 times the CMC), below which substantial beading is observed.

This indicates that micelle formation contributes as well to fiber formation and that the concentrations required are well above the CMC of the surfactant. While similar results showing surfactant-facilitated electrospinning have been reported,⁷⁴ no insight into this has been presented. Further investigation needs to be pursued along this line. On the basis of the results presented here, the presence of PEO favorably reduces surface tension, which facilitates electrospinning. Higher concentrations of alginate can be achieved by incorporating a nonionic surfactant, further reducing the surface tension of the blend.

CONCLUSIONS

Sodium alginate alone cannot be electrospun from aqueous solution; however, it can be electrospun by blending with an appropriate polymer. Our work aimed to investigate and understand the required properties of this "carrier polymer." Our results showed that alginate must be blended with a high molecular weight electrospinnable polymer as the combination of high surface tension and high electrical conductivity limited the electrospinnability of aqueous sodium alginate. Interestingly, by systematically studying PEO of various molecular weight along with PVA, electrospinnability of the carrier polymer alone does not guarantee fiber formation when blended with alginate. Both electrospinnability and high molecular weight (600 kDa) are required characteristics for the carrier polymer.

The addition of PEO, which has been shown to allow fiber formation during electrospinning, was determined to reduce electrical conductivity and surface tension of alginate solution, thereby aiding in fiber formation. However, it seems that PEO coordination of the sodium cation through its ether group ($-\text{COC}-$) did not significantly affect the electrospinnability of the blends. On the basis of the work we present here, an extremely important consideration was the molecular weight of the carrier polymer used. Although both PVA and PEO are electrospinnable polymers alone, only high molecular-weight PEO blended with alginate yielded bead-free, alginate-rich fibers. On the basis of these findings, we speculate that the PEO-PEO interactions of the high molecular-weight entangled PEO are key to "carrying" the alginate from solution to fibers during electrospinning, and these interactions dominate in the blended system.

We found, consistent with previous studies, that fiber formation is realized at an alginate:PEO ratio between 40:60 and 50:50. On the basis of our fundamental understanding of the role of PEO, we are able to increase the alginate concentration by employing a higher molecular-weight PEO: up to 70 wt % alginate using 2000 kDa PEO and, with, the addition of Triton X-100 surfactant, up to 85 wt % alginate, higher than previously reported.

ASSOCIATED CONTENT

Supporting Information

SEM micrographs of electrospun PEO of various molecular weight, additional SEM micrographs of alginate/2 M PEO

fibers, dynamic rheology of PEO and PEO/alginate systems, and solution rheology of alginate/PEO/triton systems. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: khan@eos.ncsu.edu. Phone: 919-515-4519.

Present Address

[†]C.D.S.: Dupont Central Research and Development, 200 Powder Mill Rd, Wilmington, DE 19880-0304.

Author Contributions

[§]C.D.S. and C.T. are cofirst authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported in part by the STC program of the US National Science Foundation under agreement (CHE-9876674). Discussions with Prof. Srinivasa Raghavan (University of Maryland) and Prof. Robert Prud'homme (Princeton University) are gratefully acknowledged.

REFERENCES

- (1) Fridrikh, S. V.; Yu, J. H.; Brenner, M. P.; Rutledge, G. C. Controlling the Fiber Diameter During Electrospinning. *Phys. Rev. Lett.* **2003**, *90*, 144502(4 pp.).
- (2) Li, D.; Ouyang, G.; McCann, J. T.; Xia, Y. N. Collecting Electrospun Nanofibers with Patterned Electrodes. *Nano Lett.* **2005**, *5*, 913–916.
- (3) Sun, X. Y.; Shankar, R.; Borner, H. G.; Ghosh, T. K.; Spontak, R. J. Field-Driven Biofunctionalization of Polymer Fiber Surfaces During Electrospinning. *Adv. Mater.* **2007**, *19*, 87–91.
- (4) Huang, Z. M.; Zhang, Y. Z.; Kotaki, M.; Ramakrishna, S. A Review on Polymer Nanofibers by Electrospinning and Their Applications in Nanocomposites. *Compos. Sci. Technol.* **2003**, *3*, 2223–2253.
- (5) Theron, S. A.; Zussman, E.; Yarin, A. L. Experimental Investigation of the Governing Parameters in the Electrospinning of Polymer Solutions. *Polymer* **2004**, *45*, 2017–2031.
- (6) Fong, H.; Chun, I.; Reneker, D. H. Beaded Nanofibers Formed During Electrospinning. *Polymer* **1999**, *40*, 4585–4592.
- (7) Kim, B.; Park, H.; Lee, S. H.; Sigmund, W. M. Poly (Acrylic Acid) Nanofibers by Electrospinning. *Mater. Lett.* **2005**, *59*, 829–832.
- (8) Frenot, A.; Chronakis, I. S. Polymer Nanofibers Assembled by Electrospinning. *Curr. Opin. Colloid. In.* **2003**, *8*, 64–75.
- (9) Bhattacharai, N.; Li, Z.; Edmondson, D.; Zhang, M. Alginate-Based Nanofibrous Scaffolds: Structural, Mechanical, and Biological Properties. *Adv. Mater.* **2006**, *18*, 1463–1467.
- (10) Zhang, S. G. Beyond the Petri Dish. *Nat. Biotechnol.* **2004**, *22*, 151–152.
- (11) Zhang, R.; Ma, P. X. *J. Biomed. Mater. Res.* **2000**, *52*, 430–438.
- (12) Rho, K. S.; Jeong, L.; Lee, G.; Seo, B. M.; Park, Y. J.; Hong, S. D.; Roh, S.; Cho, J. J.; Park, W. H.; Min, B. M. Electrospinning of Collagen Nanofibers: Effects on the Behavior of Normal Human Keratinocytes and Early-Stage Wound Healing. *Biomaterials* **2006**, *27*, 1452–1461.
- (13) Lim, S. H.; Mai, H. Electrospun Scaffolds for Stem Cell Engineering. *Adv. Drug Deliver. Rev.* **2009**, *61*, 1084–1096.
- (14) Li, W. J.; Laurencin, C. T.; Caterson, E. J.; Tuan, R. S.; Ko, F. K. Electrospun Nanofibrous Structure: A Novel Scaffold for Tissue Engineering. *J. Biomed. Mater. Res. A* **2002**, *60*, 613–621.
- (15) Pham, Q. P.; U. Sharma, U.; Mikos, A. G. Electrospinning of Polymeric Nanofibers for Tissue Engineering Applications: A Review. *Tissue Eng.* **2006**, *12*, 1197–1211.

- (16) Pattison, M. A.; Wurster, S.; Webster, T. J.; Haberstroh, K. M. Three-Dimensional, Nano-Structured PLGA Scaffolds for Bladder Tissue Replacement Applications. *Biomaterials* **2005**, *26*, 2491–2500.
- (17) Tuzlakoglu, K.; Bolgen, N.; Salgado, A. J.; Gomes, M. E.; Piskin, E.; Reis, R. L. Nano- and Micro-Fiber Combined Scaffolds: A New Architecture for Bone Tissue Engineering. *J. Mater. Sci.: Mater. Med.* **2005**, *16*, 1099–1104.
- (18) Li, W. J.; Danielson, K. G.; Alexander, P. G.; Tuan, R. S. Biological Response of Chondrocytes Cultured in Three-Dimensional Nanofibrous Poly(ϵ -Caprolactone) Scaffolds. *J. Biomed. Mater. Res.* **2003**, *67*, 1105–1114.
- (19) Li, D.; Xia, Y. N. Electrospinning of Nanofibers: Reinventing the Wheel? *Adv. Mater.* **2004**, *16*, 1151–1170.
- (20) Geng, X. Y.; Kwon, O. H.; Jang, J. H. Electrospinning of Chitosan Dissolved in Concentrated Acetic Acid Solution. *Biomaterials* **2005**, *26*, 5427–5432.
- (21) Toh, Y. C.; Ng, S.; Khong, Y. M.; Zhang, X.; Zhu, Y.; Lin, P. C.; Te, C. M.; Sun, W.; Yu, H. Cellular Responses to a Nanofibrous Environment. *Nano Today* **2006**, *1*, 34–43.
- (22) Almany, L.; Seliktar, D. Biosynthetic Hydrogel Scaffolds Made from Fibrinogen and Polyethylene Glycol for 3D Cell Cultures. *Biomaterials* **2005**, *26*, 2467–2477.
- (23) Sill, T. J.; von Recum, H. A. Electrospinning: Applications in Drug Delivery and Tissue Engineering. *Biomaterials* **2008**, *29*, 1989–2006.
- (24) Boland, E. D.; Pawlowski, K. J.; Barnes, C. P.; Simpson, D. G.; Wnek, G. E.; Bowlin, G. L. Electrospinning of Bioreducible Polymers for Tissue Engineering Scaffolds. *Polym. Nanofibers ACS Symp. Ser.* **2006**, *918*, 188–204.
- (25) Hsu, S. H.; Whu, S. W.; Hsieh, S. C.; Tsai, C. L.; Chen, D. C.; Tan, T. S. Evaluation of Chitosan-Alginate-Hyaluronate Complexes Modified by an RGD-Containing Protein as Tissue-Engineering Scaffolds for Cartilage Regeneration. *Artif. Organs* **2004**, *28*, 693–703.
- (26) Suh, J. K. F.; Matthew, H. W. T. Application of Chitosan Based Polysaccharide Biomaterials in Cartilage Tissue Engineering: A Review. *Biomaterials* **2000**, *21*, 2589–2598.
- (27) Langer, R.; Tirrell, D. A. Designing Materials for Biology and Medicine. *Nature* **2004**, *428*, 487–492.
- (28) Kumar, M. N.; Muzzarelli, R. A.; Muzzarelli, C.; Sashiwa, H.; Domb, A. J. Chitosan Chemistry and Pharmaceutical Perspectives. *Chem. Rev.* **2004**, *104*, 6017–6084.
- (29) Shields, K. J.; Beckman, M. J.; Bowlin, G. L.; Wayne, J. S. Mechanical Properties and Cellular Proliferation of Electrospun Collagen Type II. *Tissue Eng.* **2004**, *10*, 1510–1517.
- (30) Shih, Y. R.; Chen, C. N.; Tsai, S. W.; Wang, Y. J.; Lee, O. K. Growth of Mesenchymal Stem Cells on Electrospun Type I Collagen Nanofibers. *Stem Cells* **2006**, *24*, 2391–2397.
- (31) Sefcik, L. S.; Neal, R. A.; Kaszuba, S. N.; Parker, A. M.; Katz, A. J.; Ogle, R. C.; Botchwey, E. A. Collagen Nanofibres Are a Biomimetic Substrate for the Serum-Free Osteogenic Differentiation of Human Adipose Stem Cells. *J. Tissue Eng. Regen. Med.* **2008**, *2*, 210–220.
- (32) Dang, J. M.; Leong, K. W. Myogenic Induction of Aligned Mesenchymal Stem Cell Sheets by Culture on Thermally Responsive Electrospun Nanofibers. *Adv. Mater.* **2007**, *19*, 2775–2779.
- (33) Chen, Z. G.; Wang, P. W.; Wei, B.; Mo, X. M.; Cui, F. Z. Electrospun Collagen–Chitosan Nanofiber: A Biomimetic Extracellular Matrix for Endothelial Cell and Smooth Muscle Cell. *Acta Biomater.* **2010**, *6*, 372–382.
- (34) Wang, W.; Itoh, S.; Matsuda, A.; Ichinose, S.; Shinomiya, K.; Hata, Y.; Tanaka, J. Influences of Mechanical Properties and Permeability on Chitosan Nano/Microfiber Mesh Tubes as a Scaffold for Nerve Regeneration. *J. Biomed. Mater. Res. A* **2008**, *84A*, 557–566.
- (35) Jin, H. J.; Fridrikh, S. V.; Rutledge, G. C.; Kaplan, D. L. Electrospinning Bombyx Mori Silk with Poly (Ethylene Oxide). *Biomacromolecules* **2002**, *3*, 1233–1239.
- (36) Jin, H. J.; Chen, J.; Karageorgiou, V.; Altman, G. H.; Kaplan, D. L. Human Bone Marrow Stromal Cell Responses on Electrospun Silk Fibroin Mats. *Biomaterials* **2004**, *25*, 1039–1047.
- (37) Johnson, F. A.; Craig, D. Q.; Mercer, A. D. Characterization of the Block Structure and Molecular Weight of Sodium Algicates. *J. Pharm. Pharmacol.* **1997**, *49*, 639–643.
- (38) Moe, S.; Skjakbraek, G.; Smidsrod, O.; Ichijo, H. Calcium Alginate Gel Fibers: Influence of Alginate Source and Gel Structure on Fiber Strength. *J. Appl. Polym. Sci.* **1994**, *51*, 1771–1775.
- (39) Little, L. L.; Healy, K. E.; Schaffer, D. Engineering Biomaterials for Synthetic Neural Stem Cell Microenvironments. *Chem. Rev.* **2008**, *108*, 1787–1796.
- (40) Sennerby, L.; Rostlund, T.; Albrektsson, B.; Albrektsson, T. Acute Tissue Reactions to Potassium Alginate With and Without Colour/Flavour Additives. *Biomaterials* **1987**, *8*, 49–52.
- (41) Dar, A.; Shachar, M.; Leor, J.; Cohen, S. Optimization of Cardiac Cell Seeding and Distribution in 3D Porous Alginate Scaffolds. *Biotechnol. Bioeng.* **2002**, *80*, 305–312.
- (42) Alsberg, E.; Anderson, K. W.; Albeiruti, A.; Franceschi, R. T.; Mooney, D. J. Cell-Interactive Alginate Hydrogels for Bone Tissue Engineering. *J. Dent. Res.* **2001**, *80*, 2025–2029.
- (43) Hashimoto, T.; Suzuki, M.; Tanihara, M.; Kakimura, Y.; Suzuki, K. Development of Alginate Wound Dressings Linked with Hybrid Peptides Derived from Laminin and Elastin. *Biomaterials* **2004**, *25*, 1407–1414.
- (44) Yang, J.; Chung, T. W.; Nagaoka, M.; Goto, M.; Cho, C. S.; Akaike, T. Hepatocyte-Specific Porous Polymer-Scaffolds of Alginate/Galactosylated Chitosan Sponge for Liver-Tissue Engineering. *Biotechnol. Lett.* **2001**, *23*, 1385–1389.
- (45) Li, Z.; Zhang, M. Chitosan–alginate as scaffolding material for cartilage tissue engineering. *J. Biomed. Mater. Res. A* **2005**, *75*, 485–493.
- (46) Bhattacharai, N.; Zhang, M. Controlled Synthesis and Structural Stability of Alginate-Based Nanofibers. *Nanotechnology* **2007**, *18*, 455601 (10 pp.).
- (47) Lee, Y. J.; Shin, D. S.; Kwon, O. W.; Park, W. H.; Choi, H. G.; Lee, Y. R.; Han, S. S.; Noh, S. K.; Lyoo, W. S. Preparation of Atactic Poly(Vinyl Alcohol)/Sodium Alginate Blend Nanowebs by Electrospinning. *J. Appl. Polym. Sci.* **2007**, *106*, 1337–1342.
- (48) Safi, S.; Morshed, M.; Ravandi, S. A. H.; Ghiasi, M. Study of Electrospinning of Sodium Alginate, Blended Solutions of Sodium Alginate/Poly(Vinyl Alcohol) and Sodium Alginate/Poly(Ethylene Oxide). *J. Appl. Polym. Sci.* **2007**, *104*, 3245–3255.
- (49) Nie, H.; He, A.; Wu, W.; Zheng, J.; Xu, S.; Li, J.; Han, C. C. Effect of Poly (Ethylene Oxide) with Different Molecular Weights on the Electrospinnability of Sodium Alginate. *Polymer* **2009**, *426*–434.
- (50) Lu, J.; Zhu, Y.; Guo, Z.; Hu, P.; Yu, J. Electrospinning of Sodium Alginate with Poly (Ethylene Oxide). *Polymer* **2006**, *47*, 8026–8031.
- (51) Moon, S. C.; Ryu, B. Y.; Choi, J. K.; Jo, B. W.; Farris, R. J. The Morphology and Mechanical Properties of Sodium Alginate Based Electrospun Poly (Ethylene Oxide) Nanofibers. *Polym. Eng. Sci.* **2009**, *52*–59.
- (52) Nie, H.; He, A.; Zheng, J.; Xu, S.; Li, J.; Han, C. C. Effects of Chain Conformation and Entanglement on the Electrospinning of Pure Alginate. *Biomacromolecules* **2008**, *1362*–1365.
- (53) Klossner, R. R.; Queen, H. A.; Coughlin, A. J.; Krause, W. E. Correlation of Chitosan's Rheological Properties and its Ability to Electrospin. *Biomacromolecules* **2008**, *9*, 2947–2953.
- (54) Reneker, D. H.; Yarin, A. L.; Fong, H.; Koombhongse, S. Bending Instability of Electrically Charged Liquid Jets of Polymer Solutions in Electrospinning. *J. Appl. Phys.* **2000**, *87*, 4531–4547.
- (55) McKee, M. G.; Wilkes, G. L.; Colby, R. H.; Long, T. E. Correlations of Solution Rheology with Electrospun Fiber Formation of Linear and Branched Polyesters. *Macromolecules* **2004**, *37*, 1760–1767.
- (56) McKee, M. G.; Hunley, M. T.; Layman, J. M.; Long, T. E. Solution Rheological Behavior and Electrospinning of Cationic Polyelectrolytes. *Macromolecules* **2006**, *39*, 575–583.
- (57) Colby, R. H.; Fetter, L. J.; Funk, W. G.; Graessley, W. W. Effects of Concentration and Thermodynamic Interaction on the Viscoelastic Properties of Polymer Solutions. *Macromolecules* **1991**, *24*, 3873–3882.

- (58) Krause, W. E.; Bellomo, E. G.; Colby, R. H. Rheology of Sodium Hyaluronate under Physiological Conditions. *Biomacromolecules* **2001**, *2*, 65–69.
- (59) Graessley, W. W. Polymer Chain Dimensions and the Dependence of Viscoelastic Properties on Concentration, Molecular Weight and Solvent Power. *Polymer* **1980**, *21*, 258–262.
- (60) Rojas, O. J.; Neuman, R. D.; Claesson, P. M. Viscoelastic Properties of Isomeric Alkylglucoside Surfactants Studied by Surface Light Scattering. *J. Phys. Chem. B.* **2005**, *109*, 22440–22448.
- (61) Saquing, C. D.; Manasco, J. M.; Khan, S. A. Electrospun Nanoparticle–Nanofiber Composites via a One-Step Synthesis. *Small* **2009**, *5*, 944–951.
- (62) Rubinstein, M.; Colby, R. H.; Dobrynin, A. V. Dynamics of Semidilute Polyelectrolyte Solutions. *Phys. Rev. Lett.* **1994**, *73*, 2776–2779.
- (63) McKee, M. G.; Elkins, C. L.; Long, T. E. Influence of Self-Complementary Hydrogen Bonding on Solution Rheology/Electrospinning Relationships. *Polymer* **2004**, *45*, 8705–8715.
- (64) Talwar, S.; Hinestroza, J.; Pourdeyhimi, B.; Khan, S. A. Associative Polymer Facilitated Electrospinning of Nanofibers. *Macromolecules* **2008**, *41*, 4275–4283.
- (65) English, R. J.; Gulati, H. S.; Jenkins, R. D.; Khan, S. A. Solution Rheology of a Hydrophobically Modified Alkali-Soluble Associative Polymer. *J. Rheol.* **1997**, *41*, 427–444.
- (66) English, R. J.; Laurer, J. H.; Spontak, R. J.; Khan, S. A. Hydrophobically Modified Associative Polymer Solutions: Rheology and Microstructure in the Presence of Nonionic Surfactants. *Ind. Eng. Chem. Res.* **2002**, *41*, 6425–6435.
- (67) Tirtaatmadja, V.; Tam, K.; Jenkins, R. D. Rheological Properties of Model Alkali-Soluble Associative (HASE) Polymers: Effect of Varying Hydrophobe Chain Length. *Macromolecules* **1997**, *30*, 3271–3282.
- (68) Tang, C.; Saquing, C. D.; Harding, J. R.; Khan, S. A. In Situ Cross-Linking of Electrospun Poly (Vinyl Alcohol) Nanofibers. *Macromolecules* **2010**, *43*, 630–637.
- (69) Kim, J. H.; Min, B. R.; Lee, K. B.; Won, J.; Kang, Y. S. Coordination Structure of Various Ligands in Crosslinked PVA to Silver Ions for Facilitated Olefin Transport. *Chem. Commun.* **2002**, 2732–2733.
- (70) Kim, J. H.; Min, B. R.; Won, J.; Kim, C. K.; Kang, Y. S. Structure and Coordination Properties of Facilitated Olefin Transport Membranes Consisting of Crosslinked Poly(Vinyl Alcohol) and Silver Hexafluoroantimonate. *J. Polym. Sci., Part B* **2004**, *42*, 621–628.
- (71) McKee, M. G.; Layman, J. M.; Cashion, M. P.; Long, T. E. Phospholipid Nowoven Electrospun Membranes. *Science* **2006**, *311*, 353–355.
- (72) Manasco, J. L.; Saquing, C. D.; Tang, C.; Khan, S. A. Cyclodextrin Fibers via Polymer-free Electrospinning. *RSC Adv.* **2012**, *2*, 3778–3784.
- (73) Helgeson, M. E.; Grammatikos, K. N.; Deitzel, J. M.; Wagner, N. J. Theory and kinematic measurements of the mechanics of stable electrospun polymer jets. *Polymer* **2008**, *49*, 2924–2936.
- (74) Talwar, S.; Krishnan, A. S.; Hinestroza, J. P.; Pourdeyhimi, B.; Khan, S. A. Electrospun Nanofibers with Associative Polymer-Surfactant Systems. *Macromolecules* **2010**, *43*, 7650–7656.
- (75) Yu, J. H.; Fridrikh, S. V.; Rutledge, G. C. The Role of Elasticity in the Formation of Electrospun Fibers. *Polymer* **2006**, *47*, 4789–4797.
- (76) Fridrikh, S. V.; Yu, J. H.; Brenner, M. P.; Rutledge, G. C. Controlling the Fiber Diameter during Electrospinning. *Phys. Rev. Lett.* **2003**, *90*, 144502–1–144502–4.
- (77) Hohman, M. M.; Shin, M.; Rutledge, G. C.; Brenner, M. P. Electrospinning and Electrically Forced Jets. I. Stability Theory. *Phys. Fluids* **2001**, *13*, 2201–2220.
- (78) Bhattacharjee, P. K.; Schneider, T. M.; M.P. Brenner, M. P.; McKinley, G. H.; Rutledge, G. C. On the Measured Current in Electrospinning. *J. Appl. Phys.* **2010**, *107*.
- (79) Longenberger, L.; Mills, G. Formation of Metal Particles in Aqueous Solutions by Reactions of Metal Complexes with Polymers. *J. Phys. Chem. B.* **1995**, *99*, 475–478.
- (80) Hiemenz, P. C.; Rajagopalan, R. *Principles of Colloid and Surface Chemistry*, 3rd ed.; Marcel Dekker: New York, 1997.