**Significant Enhancement of Elasticity in Alginate-Clay Nanocomposite Hydrogels with
PEO-PPO-PEO Copolymers**

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Abstract

The mechanical properties of a new type of nanocomposite gel, consisting of varying concentrations of the biopolymer alginate and the synthetic clay Laponite®, together with the temperature-sensitive copolymer poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO, trade name Pluronic®F127), are reported. These “ALP” gels (alginate-Laponite®-Pluronic®) were prepared and studied using rheology. Gels with multiple networks and gelation mechanisms have been explored as one strategy to strengthen and stiffen conventional hydrogels, which usually consist of a single polymer network. This work shows that the ALP gels exhibit significantly higher storage and loss modulus (G' , G'') values than gels composed of only alginate and Laponite®. Moreover, the interaction between the components appears to be synergistic; that is, the resulting multicomponent hydrogels are much more elastic than the additive effects of individual components. For example, the G' of one series of the nanocomposite gels containing F127 Pluronic® experiences two orders of magnitude enhancement compared to its respective control containing only alginate and Laponite®. Furthermore, the ALP gels show a 20-40x enhancement in storage modulus, with values as high as 10,000 – 20,000 Pa, over the 30-55°C temperature range. The large degree of enhancement in the storage modulus of the ALP gels with addition of Pluronic® is quite remarkable, compared to alginate-Laponite® gels on their own at comparable concentrations and temperatures, which form relatively weak gels. These results provide a simple strategy for significantly increasing the mechanical properties of polymer hydrogels used in biomaterials applications.

Keywords: hydrogel, alginate, polymer-clay nanocomposite

Introduction

Hydrogels are three-dimensional polymer networks made up of water soluble polymers crosslinked via chemical or physical bonds. They have become widely studied due to their high water content and ability to be engineered for various biomedical applications. Traditionally, hydrogels are mechanically weak materials that are usually composed of a single network of hydrophilic polymer, which results in a hydrogel that is soft and weak. These weak gels tend to fail at tensile stress less than sub-MPa with strain less than 100%; but load-bearing biological soft tissues are much stronger (e.g. cartilage is 75% water and has compressive fractures stress of 36 MPa)[1][2][3]. Different strategies that have been investigated to improve hydrogel strength and stiffness include ionically crosslinked copolymers[4], slide ring polymer gels[5], interpenetrating hydrogels[6], double networks[7], and nanocomposite polymer hydrogels[8][9][10]. Here, we focus on hydrogels containing components with multiple gelation mechanisms. These gels are partially inspired by double network gels[1], which are comprised of both a stiff and a soft network and are formulated in a sequential method of making one network and then another. Our systems contain a network that is ionically crosslinked (alginate), synthetic clay particles (Laponite®) that may yield an associative polymer-particle network by adsorbing polymer chains onto its surface, and a thermoresponsive block copolymer (Pluronic® F127) that self-assembles into a cubic micellar gel.

These materials fall in the general category of nanocomposite polymer hydrogels, which are crosslinked polymer networks formed by chemical or physical interactions that are swollen with water in the presence of nanoparticles or nanostructures. Depending on the polymer, the crosslinked polymer network is able to respond to external stimuli (e.g. temperature, pH, composition). Nanoparticles can either crosslink the hydrogel, adsorb to polymer chains, or

introduce novel properties (e.g. added sensitivity to electrical, magnetic, mechanical, optical, thermal stimulation, etc.) to the hydrogel by being entrapped within the network[9]. Oftentimes the polymer and nanoparticles synergistically work together to produce a hydrogel that has improved biological, chemical, mechanical and physical properties.

A primary component of our systems, alginate, is a polysaccharide that is produced by certain brown algae and has been found to be biocompatible, mucoadhesive, and non-immunogenic[11][12][13]. Alginate hydrogels crosslinked with divalent and trivalent cations can be utilized for many tissue engineering applications such as for wound dressings, dental impressions, sustained release of drugs, immobilization of enzymes, injectable microcapsules, cell encapsulation and immobilization[14][15][16].

The second component of our systems, Laponite®, is a synthetic disc-shaped smectite clay that is used as a rheological modifier for applications in cosmetics, inks and paints. Structurally, it is a layered silicate colloid that has a composition and structure that closely resembles that of hectorite, which is a natural smectite clay and its empirical formula is $\text{Na}^{+}_{0.7}[(\text{Si}_8\text{Mg}_{5.5}\text{Li}_{0.3})\text{O}_{20}(\text{OH})_4]^{-0.7}$. Each crystal has a diameter of about 25nm, a thickness of about 1 nm, negative charges on its faces, and a positively-charged rim. When dispersed in water, Laponite® hydrates and swells to form a gel[17].

The third component of the gels, Pluronic® F127, belongs to a family of triblock copolymers containing poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) that have applications in controlled release due to their thermoreversible gelation[18][19]. A range of copolymers in the Pluronic® family with varying molecular weights and block ratios are commercially available, such as F127, F68, and F108. Due to its

central relatively hydrophobic PPO segment and hydrophilic PEO segments, F127 forms spherical micelles in dilute aqueous solution[20].

Studies have been done to characterize solutions of Pluronic® F127 and Laponite® and quantify the polymer-clay interactions[21][22][23]. Using small-angle neutron scattering (SANS), Nelson and Cosgrove observed Pluronic® molecules' hydrophobic PPO segments preferentially adsorb onto Laponite® surfaces, with the hydrophilic PEO segments loosely extended into solution[21]. Boucenna et al. used SANS, DSC and rheology and also found that Pluronic® copolymer unimer adsorb onto Laponite®, which disturbs the micellization and promotes structural disorder. Interestingly, although the presence of Laponite® interferes with micellization, the clay particles do not prevent gelation of Pluronic® F127[23]. Indeed, rheology, SANS, and TEM studies of Raghavan and Sun used rheology show that the presence of Laponite® can lower the F127 concentration at which thermogelling occurs[22].

Alginate/Pluronic® composite thermogels have also been explored by several groups[24][25][26]. Fang and coworkers designed an alginate-Pluronic® composite transdermal system, which showed sustained release of selegiline and showed almost no degradation[24]. Roberts and coworkers studied the transport properties of BSA and riboflavin in Pluronic® F68-alginate composite hydrogels and found that Pluronic® incorporation at concentrations above the critical micelle concentration impeded the transport of large biological molecules, which can affect release properties[25]. Previous work done by our group used calorimetry, SANS, shear rheology, unconfined compression, and fracture to study alginate/F127 composite hydrogels[26]. Compression studies showed plasticity above the lower gelation temperature. Additionally, the peaks in the scattering spectra for 1.5wt% alginate/20wt% F127 qualitatively show that F127 is able to form supramolecular associations above the critical micelle temperature while entrapped

in an alginate matrix, which is in agreement with results from rheology. The alginate matrix was observed to not hinder Pluronic® micelle formation or the self-assembly of micelles into a cubic lattice, which agrees with results from differential scanning calorimetry.

Alginate/Laponite® composites have also been prepared and characterized by several groups[27][28][29]. Nassaret. al. conducted adsorption and x-ray diffraction experiments on composites containing Laponite® with alginate and alginic acid polysaccharides and found that all composites exhibited favorable thermal and mechanical properties[27]. Moreover, the Laponite®-derived composites had high adsorption of Cr(III) and methylene blue from aqueous medium. Chrzanowskiet. al. studied the physicochemical properties and biological responses of Laponite®/alginate nanocomposites and found that Laponite® incorporation significantly improved compression strength without reducing injectability[28]. In addition, the nanocomposites were non-toxic and had improved cell viability compared to alginate alone; but, due to high degradation rates, did not support cell adhesion well. Li et. al. studied the swelling and release behavior of Laponite®/alginate hydrogels and found that under acidic conditions, the composite gels exhibited good transport characteristics for controlled delivery of cationic drugs[29].

The above studies suggest that there are synergistic interactions among alginate, Pluronic® copolymers, and Laponite® particles that lead to favorable physical properties for biomedical applications. However, to our knowledge, there has been no previous work on nanocomposite gels containing alginate, Laponite®, and Pluronic® together. This work investigates the rheological behavior of a series of different compositions of nanocomposite hydrogels containing alginate, Laponite® and Pluronic® F127 (ALP) and aims to find an optimal composition that maximizes mechanical stiffness as measured by the storage modulus.

Material and Methods

Materials

Sodium alginate, ethylenediaminetetraacetic acid calcium disodium salt (CaEDTA), and Pluronic® F127 were obtained from Sigma. D-Glucono-delta-lactone (GDL) was obtained from MP Biomedicals. The solutions were filtered with 0.45 μm ThermoScientific™ Nalgene™ polyethersulfone (PES) syringe filters with a diameter of 25 mm. These filters have been used in prior studies with Laponite® solutions, and there are no known interactions between the filter material and the Laponite® particles. All chemicals were used without further purification. All required solutions were prepared in nanopure water with resistivity set at 18M Ω -cm.

Methods

Alginate gels were prepared using a modification of a previously reported protocol [25, 30] utilizing CaEDTA and GDL to produce slow release of calcium ions into the solution, resulting in more uniform ionic crosslinking. For solution preparation, the required dry weight of CaEDTA was weighed out and dissolved in half the required amount of nanopure water and mechanically stirred. After all of the salt has dissolved, the solution was poured into a graduated cylinder and the rest of the required volume was added to make the final required concentration of CaEDTA solution. The solution was filtered and stored in the 4°C refrigerator until use. The slow-hydrolyzing GDL is prepared fresh each time before gel preparation. The required amount of GDL is dissolved in nanopure water and mixed.

Alginate-Laponite® nanocomposite gels that served as controls were prepared by dissolving a desired amount of Laponite® in water and mechanically stirring the resulting

solution for 30 minutes. The Laponite® solution was then filtered and the required amount of alginate was added to this filtered Laponite® solution and mechanically stirred overnight. These alginate-Laponite® solutions were gelled by slow *in situ* release of calcium ions with CaEDTA and GDL to prepare a homogenous hydrogel using a previously reported method for preparing alginate hydrogels[25][30]. The final solutions were poured into polycarbonate petri dishes and left for 26 hours to allow for complete crosslinking. The alginate-Laponite®-Pluronic® F127 (ALP) gels were prepared by the same method as the alginate-Laponite® nanocomposite gels, but the alginate-Laponite® gels were soaked at 4°C in a series of F127 solutions (5%, 10%, 15%, 20%, 30% w/v) for 7 days each to allow for incorporation into the hydrogel. All concentrations reported are initial concentrations. As reported by White et al.[26], some gels may shrink slightly and/or release water after formulation; however, for simplicity in comparing results of different samples, the concentrations used to formulate samples are used throughout. All samples were prepared and tested in triplicate. Sample names and compositions are shown in Table 1.

Small amplitude oscillatory shear studies were performed on a TA Instruments AR-G2 rheometer using a 40mm aluminum plate as the top geometry and a Peltier plate as the bottom geometry. Each sample was placed on the Peltier plate and the desired diameter was cut to fit the parallel plate geometry. Amplitude sweeps were performed prior to frequency sweeps to ensure that all experiments were performed within the linear viscoelastic regime at 25°C. Frequency and temperature sweeps were performed at a constant stress of 1.5 Pa. For all tests, a solvent trap was utilized to minimize sample evaporation.

Sample	Composition
0.75A1LC	0.75% Alginate + 1% Laponite®
0.75A1LF	0.75% Alginate + 1% Laponite® + 30% F127
1A1LC	1% Alginate + 1% Laponite®
1A1LF	1% Alginate + 1% Laponite® + 30% F127
1A0.75LC	1% Alginate + 0.75% Laponite®
1A0.75LF	1% Alginate + 0.75% Laponite® + 30% F127
1A0.5LC	1% Alginate + 0.5% Laponite®
1A0.5LF	1% Alginate + 0.5% Laponite® + 30% F127

Table 1. Summary of sample names and compositions.

Results and Discussion

All samples shown in the results exist as gels with the storage modulus, G' , greater than the loss modulus, G'' . Figure 1 shows the G' and G'' of 0.75% alginate + 1% Laponite® and 1% alginate + 1% Laponite® hydrogels both soaked in 30% F127 solution. Since only the concentration of alginate is varied, these results show that changing the concentration of alginate has no noticeable effect on the storage moduli of the hydrogels, which is about 10,000 Pa. Both moduli show a slight frequency dependence, indicating that there may be a slow mechanism for relaxation in these gels, possibly rearrangement or movement of Pluronic® micelles. Given that the gels contain densely-packed polymer micelles, such rheological behavior is not surprising; Semenov et al. included such an effect arising from the compression and movement of polymeric micelles in their description of the rheology of associative polymers[31]. However, the timescale for such a process, if it is occurring, is too long to be quantified in our rheological studies.

Figure 1. Dynamic rheology at 25°C of 0.75% alginate + 1% Laponite® and 1% alginate + 1% Laponite® hydrogels, both soaked in 30% F127 solution. The results demonstrate the effect of alginate. G' values are represented by filled symbols and G'' values are represented by unfilled symbols.

Figure 2 shows the G' and G'' of a series containing 1% alginate and varying concentrations of Laponite®, both without incorporation of F127 (Figure 2a) and with incorporation of F127 (Figure 2b). These results show the effect of only changing the concentration of Laponite®. The G' of gels without F127 were found to be frequency independent with a relatively low G' of around 700 Pa and 200 Pa for samples with 1% alginate and 0.5% Laponite®, and 1% alginate and 0.75% Laponite®, respectively. A higher concentration of Laponite® increases both the G' and G'' of the gel; the increase of 0.25% Laponite® resulted in a modest 500 Pa increase in the G' .

Figure 2b shows 1% alginate + 1% Laponite®, 1% alginate + 0.75% Laponite®, 1% alginate + 0.5% Laponite® hydrogels all soaked in 30% F127 solution to show the effect of Laponite® in the presence of F127. The G' of these gels were found to be slightly frequency

dependent, again possibly due to a slow relaxation from rearrangements of F127 micelles as described above. Interestingly, the results show that increasing Laponite® concentration has a non-monotonic effect on the moduli of ALP gels. Of the gels soaked in F127, the gel with the highest moduli is the 1% alginate + 0.75% Laponite® ($G' \sim 10,500$ Pa), followed by 1% alginate + 1% Laponite® ($G' \sim 8000$ Pa), and 1% alginate + 0.5% Laponite® ($G' \sim 4000$ Pa). This demonstrates that there may be an intermediate concentration of Laponite® that would result in a stronger nanocomposite gel in the presence of F127. This series of samples also shows that the composition of the gels can be varied to tune the modulus; varying Laponite® concentration enables control of the storage modulus from ~ 4000 Pa to $\sim 10,500$ Pa (Figure 2b). We qualitatively observed that having too high of a Laponite® concentration can make the gel brittle, likely lowering the effective moduli. Gels of 1% alginate + 2% Laponite® were also made but were too brittle to be handled and tested.

Figure 2. Dynamic rheology at 25°C of (a) 1% alginate + 0.5% Laponite® and 1% alginate + 0.75% Laponite® hydrogels both not soaked in 30% F127 solution, and (b) 1% alginate + 1% Laponite®, 1% alginate + 0.5% Laponite®, 1% alginate + 0.75% Laponite® hydrogels all

soaked in 30% F127 solution to show effect of Laponite®. G' values are represented by filled symbols and G'' values are represented by unfilled symbols.

Figure 3 shows the G' and G'' of (a) 1% alginate + 0.5% Laponite® hydrogels with and without the 30% F127 soak solution to show the effect of F127. The results illustrate that the F127 soak provides a large degree of enhancement for both the G' and G'' of gels of identical alginate and Laponite® composition by one order of magnitude; for the 1% alginate-0.5% Laponite® gels, ~250 Pa (-F127), ~4500 Pa (+F127); and the 1% alginate-0.75% Laponite® gels, experienced a two orders of magnitude enhancement in storage modulus, ~180 Pa (-F127), ~18,000 Pa (+F127)). Figure 4 summarizes the storage modulus at 1 Hz frequency and shows that alginate-Laponite® nanocomposite gels treated with F127 show a marked increase in storage moduli. All samples were tested in triplicate ($n = 3$) and the error bars shown in Figure 4 are standard deviations, with typical values of 10% or less. It can clearly be seen in Figure 4 that the difference in the storage modulus for the samples with F127 as compared to controls without F127 is statistically significant, with the samples soaked in F127 having storage moduli at least one order of magnitude larger than the controls without F127. The most pronounced enhancement is seen in the 1% alginate-0.75% Laponite® gels with and without F127, where the nanocomposite gels soaked in F127 have a storage modulus that is roughly two orders of magnitude greater than that of the nanocomposite gels without the F127 soak.

Figure 3. Dynamic rheology at 25°C of (a) 1% alginate + 0.5% Laponite® hydrogels and (b) 1% alginate + 0.75% Laponite® hydrogels both with and without the 30% F127 soak solution to show effect of F127. Values of G' are represented by filled symbols and G'' values are represented by unfilled symbols.

Figure 4. Summary of storage modulus, G' , at a frequency of 1 Hz.

Figure 5. Differential scanning calorimetry of alginate/Laponite® and alginate/Laponite®/Pluronic®F127 (ALP). Dashed lines represent compositions without Pluronic®F127 and solid lines represent compositions with Pluronic®F127. Representative heat flow output shows that the thermal behavior of the ALP composite gels, alginate/Laponite® gels, and neat 15% w/v Pluronic®F127 were similar.

Previous work done by our group on alginate-Pluronic® composite hydrogels showed that composite hydrogels had an order-of-magnitude increase in storage modulus and experienced a structural transition as the lower gelation temperature (LGT) of Pluronic® F127 is reached, as compared to neat alginate hydrogels due to the Pluronic® contribution to the mechanical properties[26]. Differential scanning calorimetry (DSC) was used to determine the apparent critical micelle temperature (CMT) of Pluronic®F127 within the alginate-Laponite®

matrix (Figure 5). Representative heat of flow output shows that the thermal behavior of the ALP composite gels, alginate/Laponite® gels, and neat 15% w/v Pluronic®F127 were nearly identical, implying that neither the Laponite® particles nor the presence of the alginate chains significantly impact the energetics of assembly of Pluronic® F127 chains.

The peak of neat 15% w/v Pluronic®F127 can be used to determine the Pluronic® content in the alginate/Laponite® and ALP gels. Specifically, the apparent CMT for 15% w/v Pluronic®F127 was 20.99°C, which is identical for 1% alginate/0.5% Laponite®, 1% alginate/0.5% Laponite® with 15% F127, 1% alginate/0.75% Laponite®, and 1% alginate/0.75% Laponite® with 15% F127. 1% alginate/1% Laponite® with 15% F127 showed a slight shift in the CMT at 20.94°C. Taken together, the apparent F127 concentration in all composite gels was estimated to be 15% F127, or in agreement with the highest concentration F127 soak each was subjected to. From the DSC data, Laponite® does not significantly affect the arrangement of Pluronic® micelles. Previous DSC experiments also found that the alginate network had little effect on Pluronic® assembly [26]. Although the present work does not focus on the changes in modulus over a large range of temperatures, preliminary studies as seen in Figure 6 show that there is a 20-40x enhancement in modulus observed at temperatures between 30°C and 55°C. We are currently exploring the temperature dependence over a larger temperature range and at lower Pluronic® concentrations.

291

292 **Figure 6.(a)** Temperature sweep of 0.75% alginate + 1% Laponite® and 1% alginate + 0.5%
 293 Laponite® with and without F127 soak. **(b)** G' of ALP gels relative to alginate-Laponite® control
 294 gels. G' values of gels with the F127 soak are represented by the filled symbols and G' of gels
 295 without the F127 soak are represented by the unfilled symbols.

296

297 Conclusions

298 This work describes the preparation and mechanical properties of a new type of
 299 nanocomposite gel, consisting of varying concentrations of alginate, Laponite® and Pluronic®
 300 F127, (ALP). The ALP nanocomposite hydrogels were prepared using physical association and
 301 studied using rheology. The results show that certain compositions of the nanocomposite ALP
 302 gels exhibit significantly higher storage and loss modulus (G' , G'') values than nanocomposite
 303 gels composed of only alginate and Laponite® at 25 $^{\circ}\text{C}$. Additionally, the nanocomposite ALP
 304 gels exhibit a 20-40x enhancement in modulus over the 30-55 $^{\circ}\text{C}$ temperature range, which is
 305 promising to the development of strong and 'smart' hydrogels.

We explored the mechanical contributions of each component of the nanocomposite gel and found that changes in alginate content in ALP gels yields no noticeable change in moduli. Laponite® concentration did not have a monotonic effect on the modulus. The highest concentration of Laponite® led to a more brittle gel and the lowest concentration of Laponite® was not enough to contribute to improving the stiffness of the gel; however, the intermediate concentration of Laponite® saw a comparable increase in storage modulus. Composite gels with Pluronic® F127 all had improved mechanical properties. In general, the interaction between the components appear to be synergistic; that is, the resulting multicomponent hydrogels are much more elastic than the additive effects of individual components. Interestingly, DSC results show that the presence of Laponite® and alginate do not impact assembly of the Pluronic® F127 chains, suggesting that more detailed studies of the gel structure and interactions among components are warranted. Currently, the temperature dependence of the ALP gels over a wider temperature range, the effect on moduli at lower F127 content, and determination of structure and interactions via small-angle neutron scattering (SANS) are being explored. Further work will be completed to study the temperature-sensitive structural and mechanical changes with the introduction of Pluronic® F127 to the composite gels.

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