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The effect of physiologically relevant additives on the rheological properties of concentrated Pluronic copolymer gels

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ABSTRACT

The high concentration triblock copolymer poly(ethylene oxide)$_{99}$–poly(propylene oxide)$_{69}$–poly(ethylene oxide)$_{99}$ (Pluronic F127) aqueous solutions with the addition of different components commonly used in physiologically relevant applications were characterized by rheological measurements, differential scanning calorimetry (DSC) and small angle X-ray/neutron scattering. The sol–gel transition temperature, as well as the storage modulus of the F127 solution depend both on the concentration of polymer and of clay. Above the gel transition, the storage modulus of the solutions increased with clay concentration. Yield strain is independent of polymer and clay concentrations. Two different kinds of inorganic salts, sodium chloride (NaCl) and calcium chloride ($CaCl_2$) were added into the polymer and polymer–clay solutions. The sol–gel transition temperature decreased noticeably, but the storage modulus decreased only a small amount with increasing concentration of inorganic salts. Addition of salts to polymer–clay solutions resulted in precipitation of the clays which decreased the modulus. No effect on the mechanical properties was observed with the addition of common serum proteins. However, addition of 0.5–10% glucose decreased the transition temperature between 3° and 7°, without significantly affecting the modulus. The depression of the transition temperature by glucose was similar to that found with salts and indicated that the mechanism, namely competition for water, may be similar.

1. Introduction

Highly concentrated solutions of non-ionic amphiphilic triblock copolymer poly(ethylene oxide)$_{99}$–poly(propylene oxide)$_{69}$–poly(ethylene oxide)$_{99}$ (PEO_{99}–PPO_{69}–PEO_{99}) are widely used in numerous biomedical applications, such as drug delivery vehicles, gels for replacing biological fluids such as synovial fluid and nucleus pulposus, and surfactants for emulsification of food and personal care products [1–4]. The Pluronic copolymers are popular for these applications, since their gelation properties are thermoreversible and easily controlled by varying the concentration. They are liquid below room temperature and gel at body temperature. Hence they are easily injected and once they fill the proper cavity they become gel as they reach body temperature. Furthermore the range of modulus achieved is easily superimposed on that of soft body tissues.

Numerous studies have been performed using a battery of complementary techniques [5–10] to try to understand the structure of these gels. In general, the copolymer Pluronic F127 aqueous solution is in a unimer state at low temperatures and low polymer concentration since both blocks (PEO and PPO) are water soluble at low temperatures. Increasing the temperature causes the formation of spherical micelles with a core of mainly the hydrophobic PPO blocks and a water-swollen corona of PEO blocks [5–8]. Combining small angle X-ray scattering (SAXS) and small angle neutron scattering (SANS), Wu et al. have shown that at high concentrations the micelles organized into a cubic structure [9]. Prud'homme et al. proposed that the ordered micelle structures are due to repulsive interactions among closely packed spherical micelles [10], and hence the material was a "micelle gel" as opposed to a chemical gel where the components are linked by covalent bonds.

Schmidt et al. have shown that the rheological properties of PEO can be affected by additives which compete with the polymer for hydration [3,4,11,12]. Since the corona of the micelle gel is composted of PEO, we felt that it was important to determine to which extent the Pluronic micelle gel was affected by these additives. Furthermore, since many of them are associated with physiological

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conditions, or used in the drug delivery vehicles, we felt that it was important to understand their effects, both singly and in combination. Also, most studies on Pluronic copolymers with salt or clay additives have been performed on dilute solutions where the focus was elucidating the structure of the adsorbed copolymer chains [13–16]. Here we wish to focus on concentrated solutions, which are more prevalent in drug delivery or tissue implant situations [1,18–20] and study the effect of common additives, such as clay, single and divalent salts, proteins, and glucose on modification of the rheological properties.

2. Experimental section

2.1. Materials

Pluronic F127 (12,600 Da, 70% w/w PEO) was obtained from BASF (Mount Olive, NJ, USA) and used without any further purification. The de-ionized water used was treated with Millipore-Q water purification system. Cloisite® Na^+ (CNa) was purchased from Southern Clay Products Inc. (Texas, USA). It is a natural hydrophilic mineral (Na^+-montmorillonite), which possesses a 2-to-1 layered structure with a single octahedral aluminum layer located between two layers of silicon tetrahedron, and has a nominal chemical formula of $[(Al_{1.67}Mg_{0.33})Si_4O_{10}(OH)_2]Na_{0.33}\cdot nH_2O$. Each layered sheet is about 10 Å thick with lateral dimensions of 0.4–1 μm. The high aspect ratio structure yields a specific surface area of ca. 725 m^2/g. Lucentite SWN clay (Lithium Magnesium Sodium Silicate) was purchased from KOBO Products, (New Jersey, USA). Lucentite SWN clay is synthesized by reacting magnesium silicates and alkali cations that have superior transparency, high brightness and constant quality. It has very low impurity content compared with natural clay. The inorganic salt calcium chloride ($CaCl_2$) was purchased from Fisher Chemicals (New Jersey, USA). Sodium chloride (NaCl) was purchased from J.T. Baker (New Jersey, USA).

2.2. Sample preparation

Gels were prepared on a weight basis using the cold method [16]. Concentrations of Pluronic polymer F127 and clays are expressed by weight percentage (% w/w). Pluronic polymer was dissolved in de-ionized (DI) water and stirred at 4 °C. The solution was then put into the refrigerator at 4 °C for 1–2 days until it became clear. In order to obtain a polymer–clay solution, we first dissolved clay in DI water while stirring for 24 h. In order to further exfoliate the clay, the solution was subsequently sonicated for 1 h. The DI-clay solution was placed into an ice bath and the F127 polymer was added. In order to ensure that the polymer was completely dissolved, the entire solution was then refrigerated at 4 °C.

2.3. Differential scanning calorimetry (DSC)

A Mettler Toledo DSC 821e differential scanning calorimeter was used to study the heat capacity of solutions as a function of temperature between 2 and 50 °C. The scans were carried out in a dry nitrogen environment at a constant heating rate of 2 °C/min, with an empty aluminum pan as reference.

2.4. SAXS

SAXS experiments were performed at the X3A2 State University of New York (SUNY) beamline, National Synchrotron Light Source (NSLS) at Brookhaven National Laboratory (BNL), using a laser-aided prealigned pinhole collimator [21]. The incident beam wavelength (λ) was tuned at 0.154 nm. The sample-to-detector distance was 1.09 m. The experimental data were corrected for background scattering and sample transmission.

2.5. SANS

To measure the structure of the Pluronic F127 gels, SANS experiments were performed at the National Institute of Standards and Technology reactor division. Data were collected on an area sensitive detector at the NG3 (NIST/Exxon/U.Minn) SANS beamline, with sample-to-detector distances of 2.90 m. The nominal wavelength of the neutrons was 6.00 Å with a dispersity $\Delta\lambda/\lambda$ of 0.10 and an average incident intensity of approximately 35,000 neutrons/s, the accessible range in q 0.0054–0.1366 A^{-1}, and the magnitude of the scattering vector defined by $(4\pi/\lambda)\sin(\theta/2)$, where θ is the angle between incident and scattered beams. A small aperture of approximately 1 cm in diameter was placed before the sample to limit the width of the diffraction spots. The samples were placed inside a sample holder designed for SANS experiments. The sample thickness was 1 mm. Samples were loaded carefully at 2 °C to minimize the shear effects, and then the temperature was increased to the test temperature 37 °C where they were stabilized for 20 min.

2.6. Rheological measurements

Rheological measurements of polymer gels were performed on a strain-controlled rheometer, Rheometrics Fluids Spectrometer II, using concentric cylinders, with an inner diameter of 16.5 mm, an outer diameter of 17.1 mm and 13.7 mm height. Temperature control was achieved using a fluid bath surrounding the outer cylinder. The concentric cylinder geometry was loaded with the polymer solutions at 2 °C, in order to ensure that they were in the liquid state. Temperature sweep measurements were performed at a constant heating rate of 1 °C/min. Low viscosity silicone oil was added to the surface of the sample to minimize the evaporation of the solvent.

The instrument was used in the oscillatory mode, in which the outer cylinder is rotated sinusoidally at a given frequency. The frequency dependence of the complex modulus was determined between 0.01 and 100 rad/s. The sol–gel transition temperature of F127 gels was determined from an oscillatory shear temperature sweep at 1 rad/s. The sol–gel transition temperature was measured for all the gels, as the temperature at which G' was half of the value for the high-temperature gel [22]. A parallel plate set up for the strain sweep test was used to obtain enough torque. In this case, we were just looking for the yield of the system, rather than absolute evaluation of the magnitudes.

3. Results and discussion

3.1. Differential scanning calorimetry

DSC measurements were carried out on block copolymer solutions as a function of polymer concentration. In Fig. 1, we see that there is a large endothermic peak observed in all spectra and the position of the peak is concentration dependent. The origin of the DSC peak was assumed to be caused by desolvation of the PPO groups [7,8]. Desolvation is also responsible for rendering the PPO hydrophobic at higher temperatures and, hence in the case of the block copolymer solutions, is also known to be responsible for formation of micelles where the core is PPO and the corona is composed of the hydrophilic PEO block. The peak is somewhat broad due to the fact that the copolymer we used has a relatively broad polydispersity of $M_w/M_n \sim 1.6$. Hence in Fig. 2 we plot the position of the peak or the micellization temperature as a function of polymer concentration. The figure shows the micellization temperature decreases linearly with increasing concentration, as expected [8] since the increased polymer concentration also decreases the entropy of micellization. It is interesting to note in Fig. 1 that a small endothermic peak appears approximately 5° above the micellization transition. This peak is only observed for

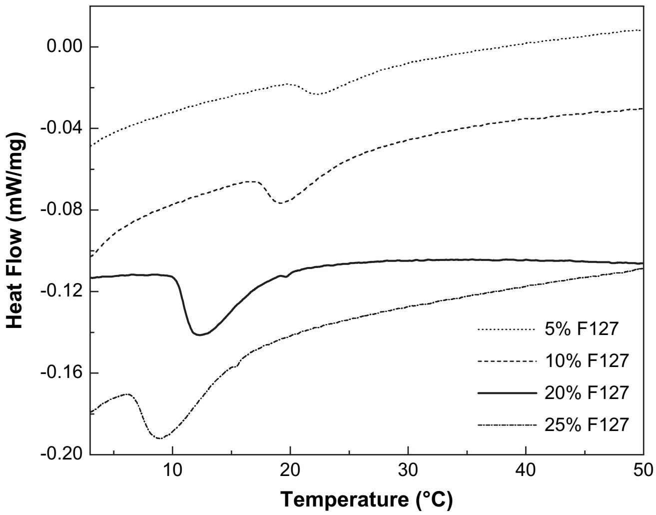

Fig. 1. DSC measurements on the different concentration solutions of Pluronic F127.

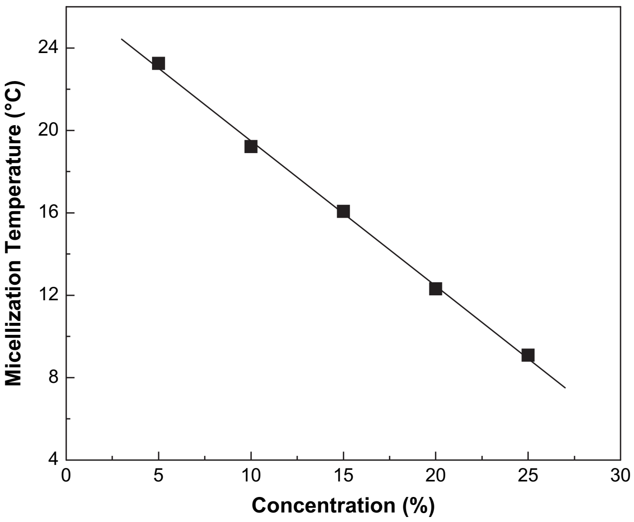

Fig. 2. Micellization temperature as a function of the Pluronic F127 concentration.

concentrations greater than 15% and corresponds to the formation of a micelle ordered phase from the isotropic micellar solution.

In Fig. 3(a), the DSC spectra obtained with the addition of CNa clay. The clay has no effect on the thermodynamic response of the gel. On the other hand in Fig. 3(b), the data obtained when 1% (NaCl and CaCl$_2$) salts are added to the polymer. The decrease of the micellization temperature can be significantly affected by the concentration of salts. From these data we can conclude that the presence of salt enhances the desolvation of PO since Na$^+$ may displace the water hydrogen bonded to the other oxygen on PO. Even though Ca^{2+} is a divalent ion, which was expected to affect micellization, the Na$^+$ ions were more effective apparently because they are more active in desolvation. It is interesting to note that even though a significant amount of Na$^+$ is present in clays (CNa and SWN) it does not affect the micellization temperature. This indicates that Na$^+$ is bound to the clay and does not displace water on the polymer. Furthermore, since the clay does not affect the yield strain, we suspect that only minimal interactions between the clay and the block copolymer exist.

3.2. SAXS and SANS: the effect of addition of clays and salts on the structure of the gels

Structural studies on Pluronic F127 gels were performed using SAXS and SANS. Fig. 4 shows the SAXS intensity profile of 30% F127

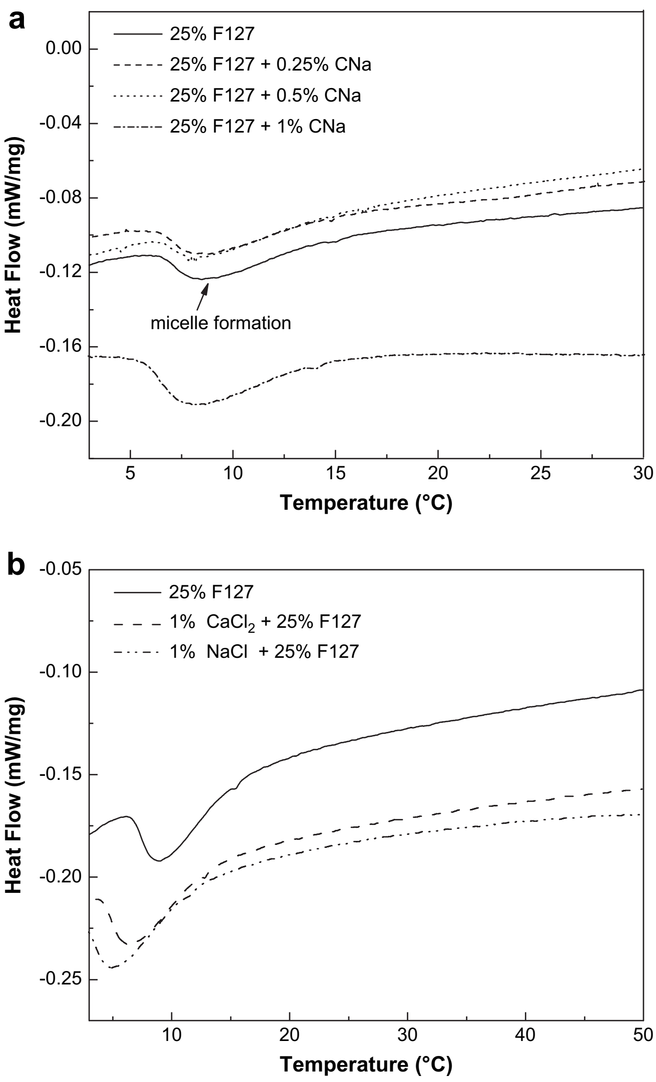

Fig. 3. (a) DSC measurements on 25% F127 with CNa clay. (b) DSC measurements on 25% F127 with CaCl$_2$ and NaCl salts.

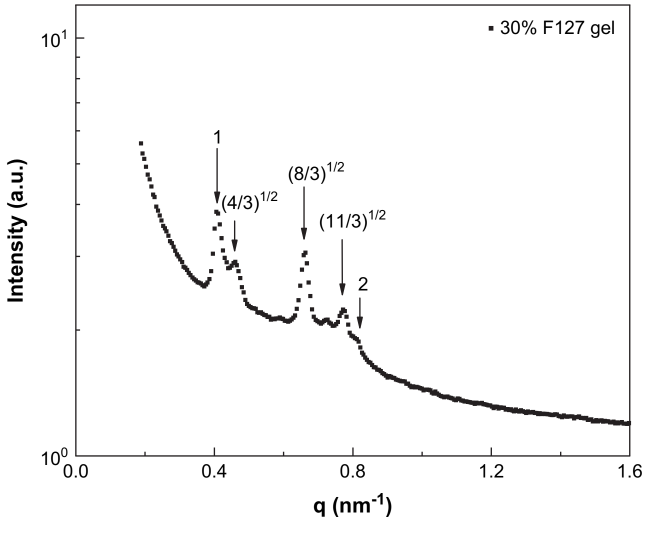

Fig. 4. SAXS intensity profile of 30 wt% F127 in H_2O at 37°C. The arrows indicate the peak positions. The numbers represent the ratio of the peak position relative to the first order peak.

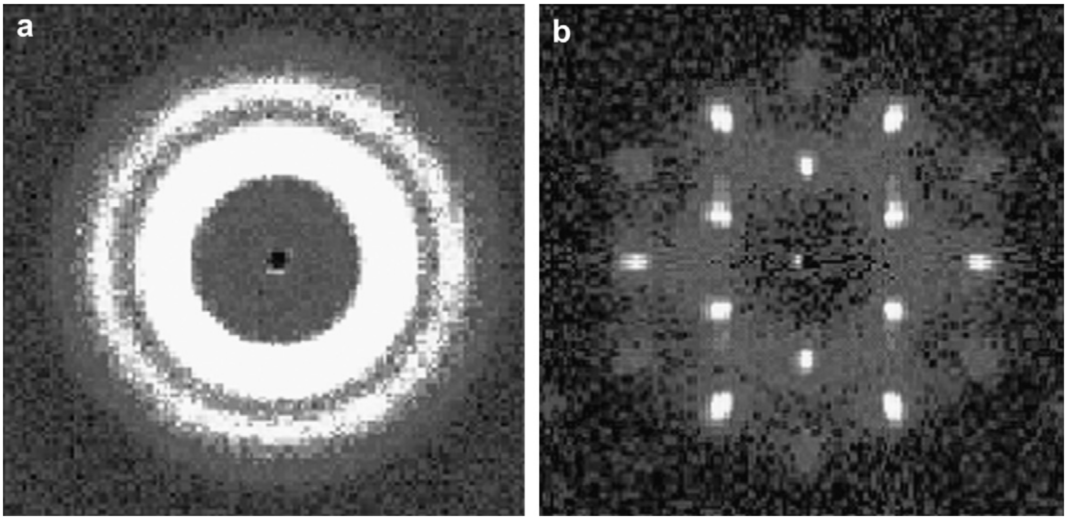

Fig. 5. SANS intensity patterns of (a) 30 wt% F127 in D_2O; (b) 30 wt% F127 with 1 wt% NaCl in D_2O.

in H_2O, showing the usual ring structure already reported by Wu et al. [9]. On the basis of the Bragg diffraction peaks from SAXS we are able to determine that the F127 gel structure as a polycrystalline face-centered cubic (FCC) lattice. The corresponding diffraction planes can also be indexed as (111), (200), (220), (311) and (222), which were also consistent with SAXS data reported by Wu et al. In Fig. 5(a) and (b), the SANS intensity patterns of 30% F127 gel in D_2O and 30% F127 gel with 1% NaCl added in D_2O, respectively. Compared with Fig. 5(a), from (b) we can see that in this case a highly oriented crystalline pattern was found which means that the complete irradiated volume formed one crystalline-domain. The pattern can be interpreted in terms of a stacking of 2D hexagonally packed layers of micelles [23]. The layers of micelles were perpendicular to the beam. By fitting the positions of the diffraction peaks, we deduced that the micelles had a distance of 19.2 nm between two nearest neighbor micelles, which is similar with what was found for the polycrystalline gel without salt. Salts are known to reduce the solvent quality of water for both PEO and PPO.

3.3. The effects of added salts and clays on the rheological properties

To measure the linear viscoelastic properties, it is necessary to determine the linear viscoelastic region. This region was determined by measuring the storage modulus G' and the loss modulus G'' as a function of the strain amplitude, using a 30% F127 gel. The strain amplitude sweep was measured between 0.0003 and 0.01 at 1 rad/s. From Fig. 6, it was observed that G' is independent of strain amplitude up to 0.01. Therefore, a strain amplitude of 0.001 at 1 rad/s shear rate was used for all the dynamic measurements, in order to remain in the linear regime and preserve the internal structure.

Fig. 6 shows the CNa clay effects on the yield strain of the gels. The yield strain did not increase with increasing clay concentration, even though CNa clay is known as a viscosity modifier for water since it can exfoliate and form a gel.

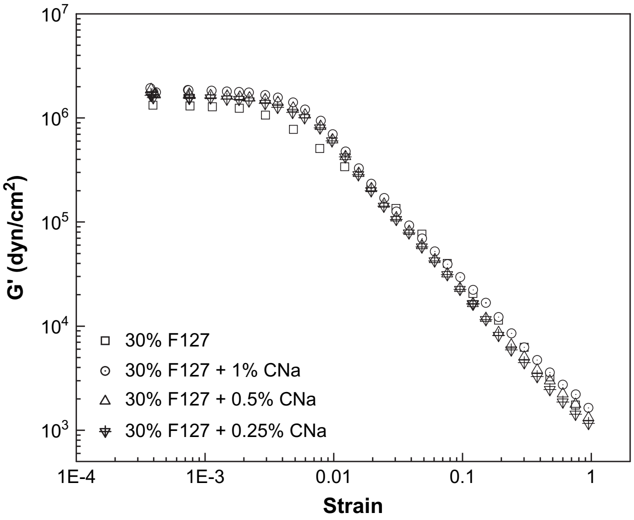

Fig. 6. Storage modulus as a function of strain for gels with 30 wt% Pluronic F127 with and without Cloisite Na^+ (CNa) clay. The oscillating frequency is 1 rad/s and temperature is 37 °C. All have yield strain ~0.005.

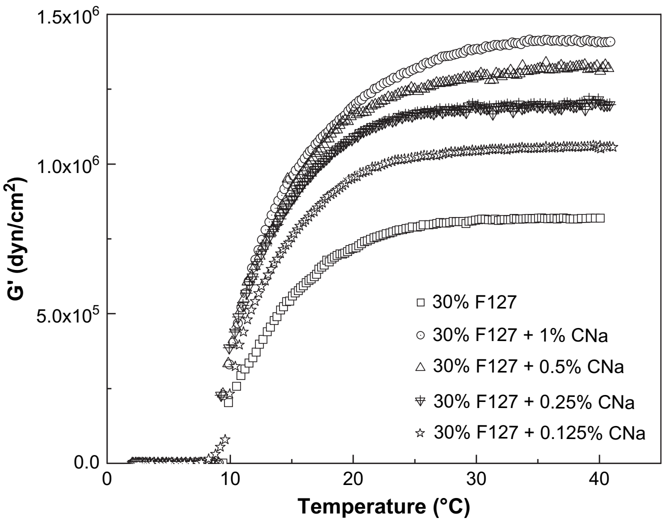

Fig. 7. Storage modulus of 30% F127 during heating at 1 °C/min, with and without Cloisite Na^+ clay at a frequency of 1 rad/s and strain of 0.001.

The temperature dependence of rheological properties of the gels was studied at a range of 2–40 °C. In Fig. 7, we plot the storage modulus G' as a function of temperature. The storage modulus is low at low temperature but it increases dramatically with increasing temperature as a result of the gel forming process. At the end of the sol–gel transition, G' plateaus become independent of the temperature. The effect of the clay concentration on the storage modulus and the sol–gel transition temperature of the gels is

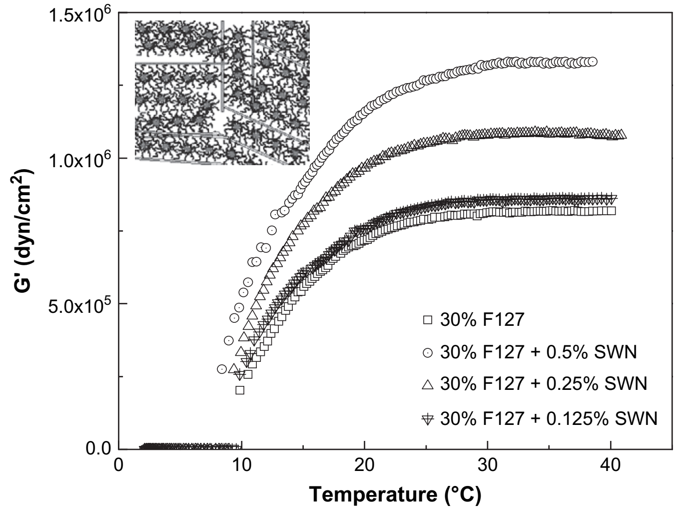

Fig. 8. Storage modulus of 30% F127 during heating at 1 °C/min, with and without SWN clay at a frequency of 1 rad/s and strain of 0.001. The cartoon in the inset shows the ordering of the clay platelets may confine the micelles and induce micelle ordering at a lower temperature.

shown in Figs. 7 and 8 for the systems with CNa and SWN clays, respectively. The two clays behaved in a similar manner; the sol–gel transition temperature decreased and *G*′ increased with the increasing concentration of both clays (see Table 1). Since both CNa and SWN clays are hydrophilic, they are able to form hydrogen bond with water molecules. It is known that when the clay concentration exceeds ~2% they are able to form a gel at temperatures as low as 4 °C due to charge–charge interactions. As can be seen from Fig. 3 this gelation does not affect the micellization temperature of the polymer, as expected, since it does not interact very strongly with the polymers. The ordering of the clay platelets may confine the micelles and induce micelle ordering at a lower temperature, as illustrated in the inset of Fig. 8. The ordering of the clay will not affect the yield point since no additional entanglements between the micelles occurred. On the other hand, the presence of the clay provides resistance to the shear, hence effectively increasing the modulus of the solution.

The solubility, rheological properties and the gelation process of the Pluronic F127 in water can be changed in the presence of inorganic salts such as NaCl and $CaCl_2$. The storage modulus as a function of temperature for the 30% F127 gel with different concentrations of NaCl and $CaCl_2$ are shown in Figs. 9 and 10, respectively. The sol–gel transition temperatures and the storage modulus (listed in Table 2) slightly decreased with increasing concentration of either NaCl or $CaCl_2$. The possible explanation for these phenomena is: when the salts of NaCl and $CaCl_2$ form ions in water, the water molecules have more affinity for ions than the polymer molecules. In this case there is a decrease in the quantity of free water molecules. This system also has less water molecules to form bonds with the polymer molecules and the gelation process occurs at a lower temperature. The slightly decreased storage modulus of the solution containing NaCl and $CaCl_2$ is caused by a reduction in solubility of PEO in water, shrinking the micelle

Table 1
The storage modulus (37 °C) and sol–gel transition temperature for the Pluronic F127-clay gels

	Clay concentration (%)	F127 concentration (%)	Storage modulus (dyn/cm^2)	Sol–gel transition temperature (°C)
SWN	0.00	30	8.17E-05	14.2
	0.13	30	8.65E-05	12.4
	0.25	30	1.09E-06	12.0
	0.50	30	1.33E-06	11.3
CNa	0.13	30	1.05E-06	13.2
	0.25	30	1.20E-06	12.7
	0.50	30	1.32E-06	12.4
	1.00	30	1.41E-06	11.8

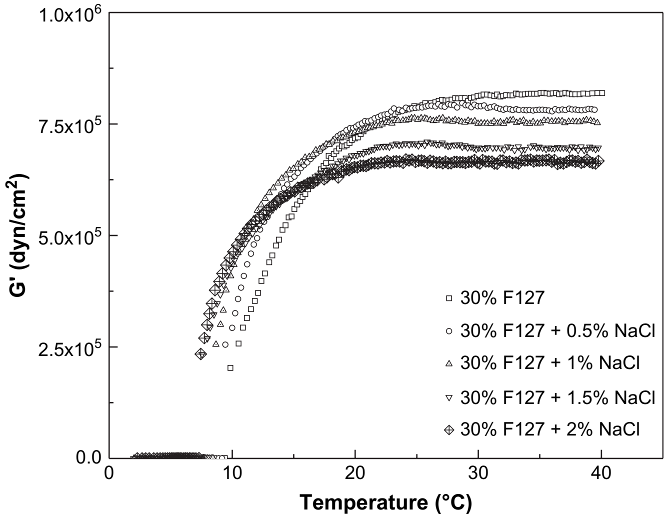

Fig. 9. Storage modulus of 30% F127 during heating at 1 °C/min, with and without NaCl at a frequency of 1 rad/s and strain of 0.001.

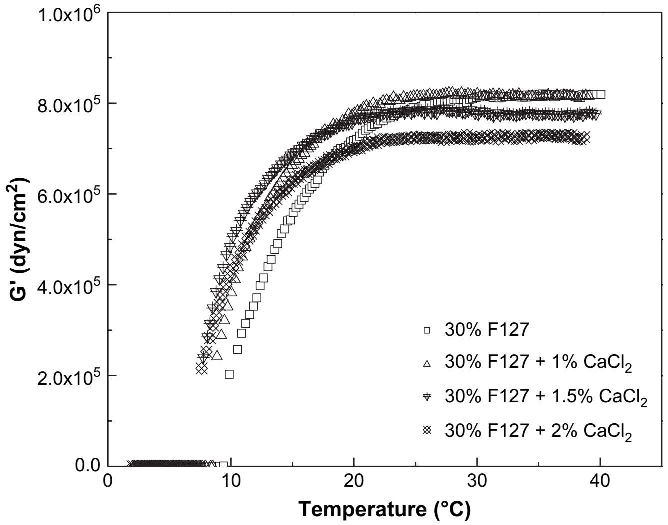

Fig. 10. Storage modulus of 30% F127 during heating at 1 °C/min, with and without CaCl2 at a frequency of 1 rad/s and strain of 0.001.

Table 2
The storage modulus (37 °C) and sol–gel transition temperature for the Pluronic F127-salt gels

	Salt concentration (%)	F127 concentration (%)	Storage modulus (dyn/cm^2)	Sol–gel transition temperature (°C)
NaCl	0.00	30	8.17E-05	14.2
	0.50	30	7.94E-05	11.6
	1.00	30	7.63E-05	10.4
	1.50	30	7.06E-05	9.5
	2.00	30	6.66E-05	8.7
$CaCl_2$	0.00	30	8.17E-05	14.2
	1.00	30	8.17E-05	11.3
	1.50	30	7.78E-05	10.0
	2.00	30	7.23E-05	9.6

corona. The thermoreversible gelation behavior is generally accepted as a result of micellar close packing [9,10]. When the salts are added into the solutions, the micelles become more densely packed, occupy less volume in solution and are less likely to come into contact and entangle with each other, consequently leading to weakened storage modulus of the gels.

In Fig. 12, we compare the effect of increasing the concentrations of clays and salts on the storage modulus. The clay has a much larger effect on the modulus than the salts. G' increased by nearly a factor of two when the concentration of clay was increased to 1% and decreased by 10% when the concentration of either salt was increased to 2%. In Fig. 13, we summarize the different effects of clays and salts on the sol–gel transition temperature, where both salts and clays are effective in decreasing the transition temperature. In the case of salts, the decrease was described as being due to the ‘salting out’ effect where the salt and polymer compete for the water molecules.

3.4. *The effect of glucose and proteins*

Glucose and proteins are also common components in serum and hence should be considered when placing F127 in physiological conditions. Fig. 11(a) and (b) shows the data for G' as a function of concentration for BSA and Lysozyme proteins. They neither affect the modulus nor the transition temperature of a 30% F127 gel. Both proteins remain in solution and yet do not appear to interact significantly with the micelle gel. Jiang et al. have shown that even concentrations as small as 0.5% of multiblock copolymer can have a large affect on G' of the micelle gel [24], due to the formation of a reinforcement network as the copolymer brings together adjacent micelles. Since proteins are amphiphilic and have hydrophobic and hydrophilic segments, it was postulated that may have a similar effect. This data show the contrary, and hence these hydrogels can be used in the presence of proteins without change in their mechanical properties.

Glucose on the other hand, does affect the rheological properties. Fig. 11(c) shows G' for a 30% solution as a function of glucose concentration. The concentrations shown here correspond to those typically associated with diabetes in humans. From the figure we see that G' is not affected, on the other hand glucose is the most effective of all the compounds tried in lowering the transition temperature. This is shown in Fig. 13 where glucose is even more effective than salts in reducing the transition temperature. Glucose, in a manner similar to salt, competes for water with the hydrogel and hence this effect is similar to the “salting out” phenomenon previously discussed.

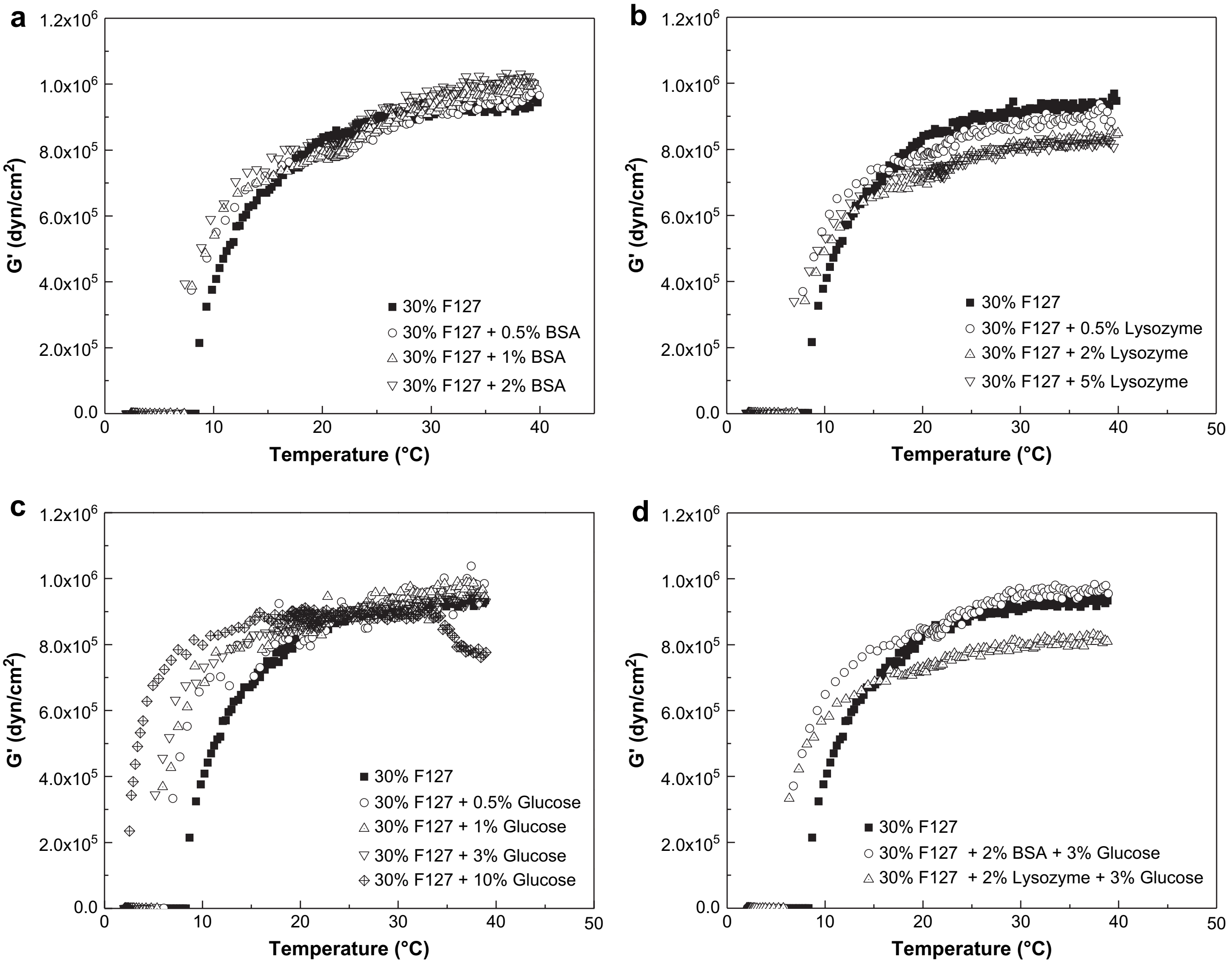

Fig. 11. (a) Storage modulus of 30% F127 during heating at 1 °C/min, with and without BSA at a frequency of 1 rad/s and strain of 0.001. (b) Storage modulus of 30% F127 during heating at 1 °C/min, with and without Lysozyme at a frequency of 1 rad/s and strain of 0.001. (c) Storage modulus of 30% F127 during heating at 1 °C/min, with and without glucose at a frequency of 1 rad/s and strain of 0.001. (d) Storage modulus of 30% F127 during heating at 1 °C/min, with and without BSA, Lysozyme and glucose at a frequency of 1 rad/s and strain of 0.001.

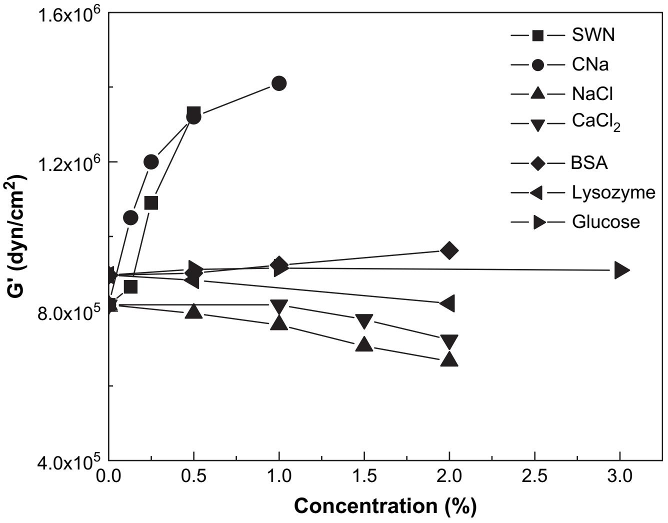

Fig. 12. Storage modulus of the gel as a function of the additive concentration. Clays raise the modulus; salts subtly lower the modulus; while the proteins and glucose have little effect on the modulus.

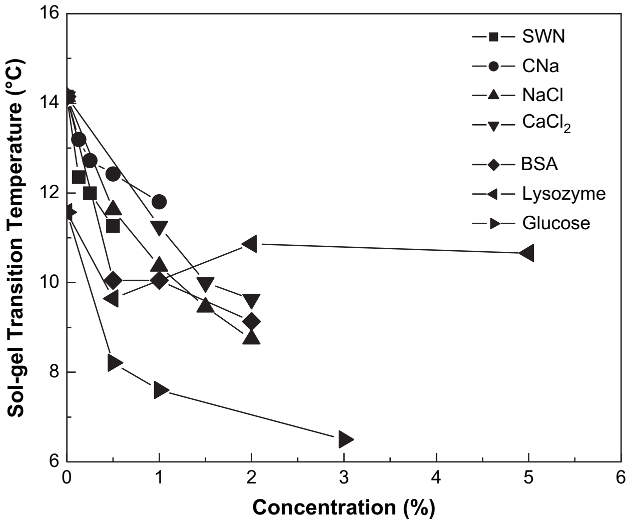

Fig. 13. The sol–gel transition temperature as a function of the additive concentration.

Non-enzymatic glycation is a well-known phenomenon where glucose is known to combine with proteins. Hence we also tested the response of F127 with a combination of the two proteins used with glucose. Fig. 11(d) shows that the effects are completely additive and that no synergy occurs when the two components are combined.

4. Conclusion

The effect of physiologically relevant additives on the rheological properties of concentrated Pluronic copolymer Gels was characterized by rheological measurements, differential scanning calorimetry (DSC) and small angle X-ray/neutron scattering. The sol–gel transition temperature, and the storage modulus of the F127 solution were found to depend both on the concentration of polymer and of clay. Above the gel transition, the storage modulus of the solutions increased with clay concentration. No change was observed for the yield strain of the polymer–clay gels. Two different kinds of inorganic salts, sodium chloride (NaCl) and calcium chloride ($CaCl_2$) were added into the polymer and polymer–clay solutions. The sol–gel transition temperature and storage modulus of these systems decreased only a small amount with increasing concentration of inorganic salts. Addition of salts to polymer–clay solutions resulted in precipitation of the clays which decreased the modulus. Neutron scattering was performed on 30% F127 in DI water, with 1% NaCl. In each case the scattering patterns corresponded to one crystal in the scattering volume with a distance of 19.2 nm between closely packed micelles. Addition of proteins, namely BSA and Lysozyme, common components of human serum, had no effect on the rheological response. A much larger effect was observed with the addition of glucose, which lowered the transition temperature by 5 °C at a concentration of 3%, or the value associated with diabetes. Addition of both proteins and glucose did not produce any collective effects. These results show that careful consideration of salt and glucose concentrations must be made in order to use F127 under physiological conditions.

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