

Rheological Behavior of Poloxamer 407 Solution and Effect of Poly(ethylene glycol) on the Gelation

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ABSTRACT—The rheological behavior of poloxamer 407 solution as function of concentration and temperature was evaluated by rotational viscometer. The viscosity of poloxamer 407 solution was increased as the concentration of poloxamer 407 and temperature increased. At 4°C, poloxamer 407 solution showed the Newtonian flow characteristics regardless of concentration. Upon increasing temperature the poloxamer solution changed to the pseudoplastic flow pattern. And at gelation temperature, rheological profiles showed the abrupt increase in viscosity. Gelation temperature was decreased as the concentration of poloxamer 407 increased, while it increased as the concentration of poly(ethylene glycol) 4000 increased. Poly(ethylene glycol) might be expected to reduce the driving force for hydrophobic interaction resulting in slow gelation. From the viscoelastic properties of poloxamer gel system, we obtained the storage and loss modulus depending on the shear stress and frequency. And the sol-gel transition temperature was also obtained from the viscoelastic properties of poloxamer 407 gel.

Key words—Poloxamer 407, Rheology, Viscoelasticity, Gels, Gelation temperature

Introduction

Poloxamer 407 is a commercially available triblock copolymer of poly(oxyethylene/oxypropylene/oxyethylene) (PEO/PPO/PEO) having a molecular weight of 11,500 and a PEO/PPO ratio of 2:1 by weight. It has been employed for the dermatological use,¹⁾ topical ophthalmic administration²⁾ of drugs and mucoadhesive gel.^{3,4)} In a previous work,⁵⁾ poloxamer 407 was used to improve the solubility of hydrophobic drug, piroxicam using solubilizing capacity of poloxamer. It has a characteristics of a temperature-dependent sol-gel transition that affects its rheological properties.

Rheological study may be effectively employed to gain an understanding of the structure of gel system. Poloxamer solutions at concentration of 20% or above form a gel on warming to room temperature by undergoing a sol-gel transition. This thermoreversible gelation has been applied to the transdermal and controlled delivery of drugs.^{1,6)} It has been observed that the poloxamer will aggregate with an increase in solution temperature or concentration. In the low temperature region, poloxamers exist as unimers. Upon warming, an equilibrium between unimeres and micelles is established, and finally aggregates are formed at higher temperatures.⁷⁾ These aggre-

gate arise as a result of dehydration of the PPO moieties, and are assumed to consist of a PPO core surrounded by a cornea of PEO.⁸⁾ The absence of a detailed study of the rheological behaviors of poloxamer 407 solutions as a function of temperature may be partly responsible for the controversy that still exists concerning the gelation mechanism of these colloidal systems.^{9,10)}

We report here the effect of rheological properties of poloxamer 407 gel on the temperature and concentration of poloxamer 407 during gelation and dehydration process and the effect of poly(ethylene glycol) (PEG) 4000 on the gelation of poloxamer 407 solution.

Materials and Methods

Materials

Poloxamer 407 was obtained from BASF (Germany). PEG was obtained from Aldrich (U.S.A.). All other reagents were of analytical grade and were used without further purification.

Preparation of poloxamer gels

The cold technique was used to prepare the poloxamer gels.¹¹⁾ Briefly, aqueous solutions of poloxamer 407 were prepared by stirring of the sample in cold distilled water. The solution was left overnight in a refrigerator to dissolve completely. The gels were formed on warming to the room temperature depending on the concentration of poloxamer.

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Determination of gelation temperature

Poloxamer solution placed in a thermostat water bath was heated at a constant rate with constant stirring. When the stirring was stopped due to gelation, the temperature displayed on the high precision thermometer was determined as a gelation temperature.⁹⁾

Measurement of viscosity

A rotational viscometer (Haake VT500) was used to measure the viscosity of poloxamer solutions. The viscometer was programmed to run at speeds in the range 2 to 200 rpm in steps. Shear stress or viscosity depending on the shear rate was measured. Temperature was controlled at 30 to 45°C by a constant temperature circulator. Viscoelastic properties of poloxamer were determined by a parallel plate rheometer (Rheometrics Rhios v4.3.2). The diameter of the plate was 40.0 mm and the gap of the space between sample and the plate was 1.778 mm. The stress response of a viscoelastic poloxamer gels subjected to a sinusoidal strain was monitored as a function of frequency. Oscillatory tests comprised strain amplitude sweep tests and frequency sweep tests.

Results and Discussion

Viscosity of poloxamer 407 solution was determined depending on the temperature and concentration of poloxamer 407. As shown Figure 1, the viscosity was increased as the temperature and poloxamer 407 concentration increased. And the abrupt viscosity increased at certain temperature except for 10%(w/w) solution. This temperature dependence of polox-

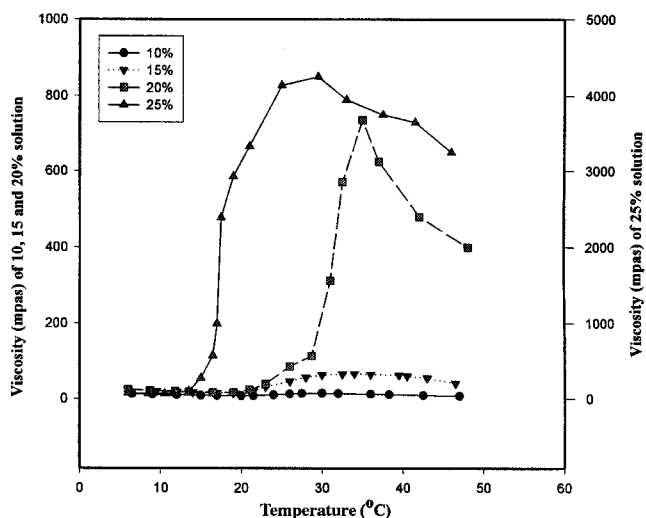


Figure 1—Viscosity of poloxamer 407 solution depending on the temperature and concentration.

Table 1—Gelation temperature of poloxamer 407 depending on the concentration of poloxamer 407 and polyethylene glycol 4000

Concentration poloxamer (%w/w)	Gelation temp. (°C)	Concentration of PEG (%w/w)	Gelation temp. (°C)
10	—	0	17.0
15	32.5	1	17.5
20	25.5	3	20.5
25	17.0	5	28.0

amer may be correlated with the gel transition of poloxamer depending on temperature. The gelation temperature of poloxamer 407 was shown in Table I. Gelation temperature was decreased as concentration of poloxamer 407 increased. Correlation of gelation and rheological properties of poloxamer 407 may be explained as following. At temperatures between 4 and 10°C, it corresponds to Newtonian fluid, indicating no reduction in intermolecular interaction for shear thinning at the higher shear rate. Below 10°C, the poloxamer chain exist as extended coils and are surrounded by a hydration layer.¹⁰⁾ The molecular arrangement is more or less regular, which is so-called unimer region. However, at the higher temperatures, the hydrogen bonding between PPO units and water becomes unstable which leads to desolvation. Thus, the structure of solution shows a more random pattern and contributes to the increase in solution entropy. The polymer chains therefore approach closer which increases the number of interactions between polymer chains. This was reflected by the increase in viscosity. Above 10°C, it corresponded to pseudoplastic or shear thinning fluid, indicating some intermolecular interactions were present and responsible for shear thinning. The 10 to 18°C temperature range corresponded to the transition region. Therefore, the boundary between the transition and micelle regions could be regard as around 18°C. As the temperature approaches 30°C, the molecular structure of the gel did not change with increasing temperature.

The initial viscosity change of poloxamer 407 solutions was shown in Figure 2. The viscosity of these solutions was plotted against temperature, giving rise to biexponential relationships in the case of 25% solution. It is characterized by a decrease in viscosity which is probably explained by the rise in activation energy resulting from the increase in temperature.¹²⁾ The phenomenon was considered as concentration-independent since the decreases rates appear similar. Contrarily, the second part of the curve showed an exponential increase in viscosity at a concentration-dependent rate. Such a relationship was in accordance with the sol-gel transition. The steep increase in

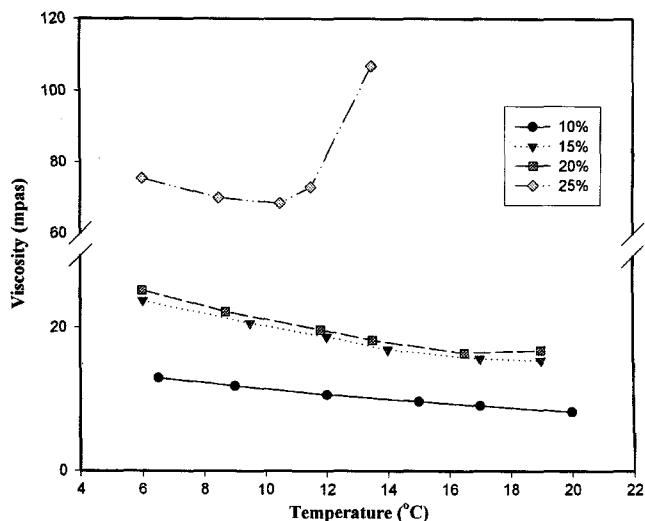


Figure 2—Initial viscosity change of poloxamer 407 solution depending on the temperature before gelling.

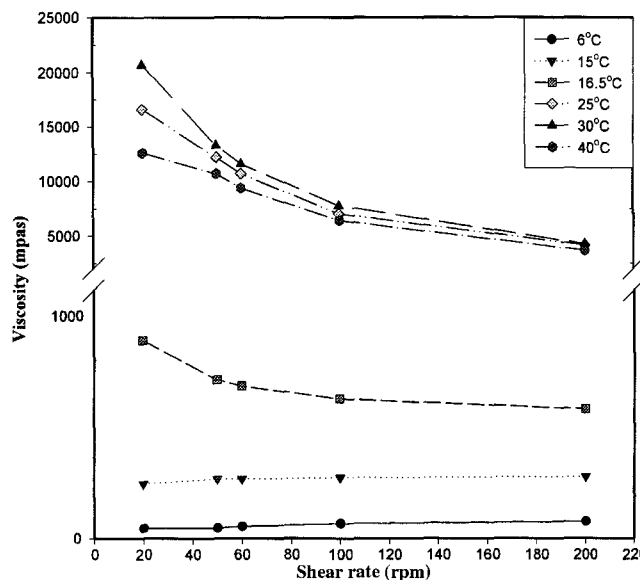


Figure 4—Viscosity of 25% poloxamer 407 solution depending on the shear rate at various temperature.

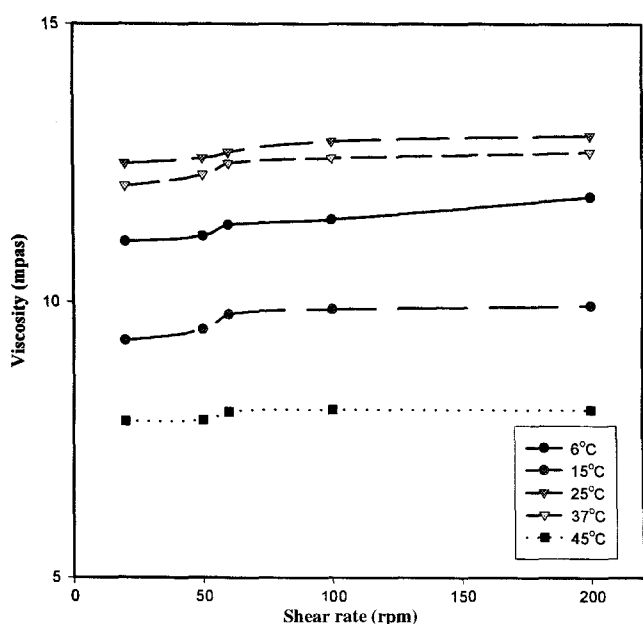


Figure 3—Viscosity of 10% poloxamer 407 solution depending on the shear rate at various temperature.

viscosity close to the gel point was attributed to the proximity of micelles and micelle entanglement. Gel state rheological properties was rather controlled by close packing of micelles and micelle entanglements which are most characteristic of polymer architecture.

Figures 3 and 4 show the viscosity of poloxamer gel depending on the shear rate at various temperatures. The system of poloxamer 10% solution displayed Newtonian behavior with a linear relationship existing between shear rate and shear stress as shown in Figure 3. But, the system of poloxamer 25% solu-

tion had different profile, that is, on increase of shear rate, the viscosity of the poloxamer was decreased showing a non-Newtonian flow as shown in Figure 4. It is well known that the temperature can dramatically influence the viscosity of fluid. The usual approach is to utilize the Arrhenius equation, $\eta = A \exp(E/RT)$ where η is the viscosity at a particular shear rate, E is the fluid-flow activation energy, T is the temperature, R is the universal gas constant, and A is a fitting parameter. In a previous result,¹³⁾ poloxamer solution at 4°C was exhibited Newtonian behavior, indicating no reduction in intermolecular interaction for shear thinning at higher shear rate. On the other hand, at 25% solution, it showed that as shear rate increased, the viscosity decreased above 15°C. The decrease in viscosity of the solution upon warming was attributed to an increase in micellization and a decrease in solvent viscosity.⁷⁾

Figure 5 shows the effect of polyethylene glycol 4000 on the viscosity of poloxamer 407 solution. Viscosity was decreased as the concentration of PEG 4000 increased. Also, the gelation temperature was increased as the concentration of PEG 4000 increased as shown in Table 1. The changes were due to the disruption of the hydration sphere presumably around the hydrophobic portion of the molecules.¹⁴⁾ PEG was expected to perturb the hydration sphere, thus lowering the local higher water molecules and consequently reducing the driving force for hydrophobic interaction and increasing the gelation temperature.

The viscoelastic property of poloxamer gel at 25°C was observed as shown in Figures 6 and 7. Storage modulus (G') is

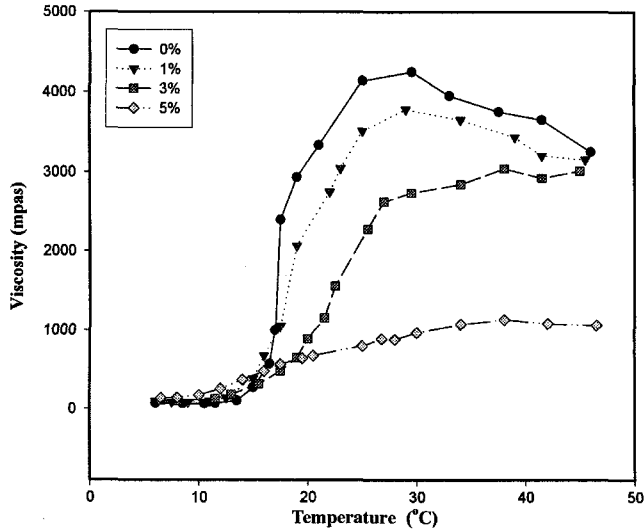


Figure 5—Viscosity of 25% poloxamer 407 solution depending on the temperature and concentration of poly(ethylene glycol) 4000.

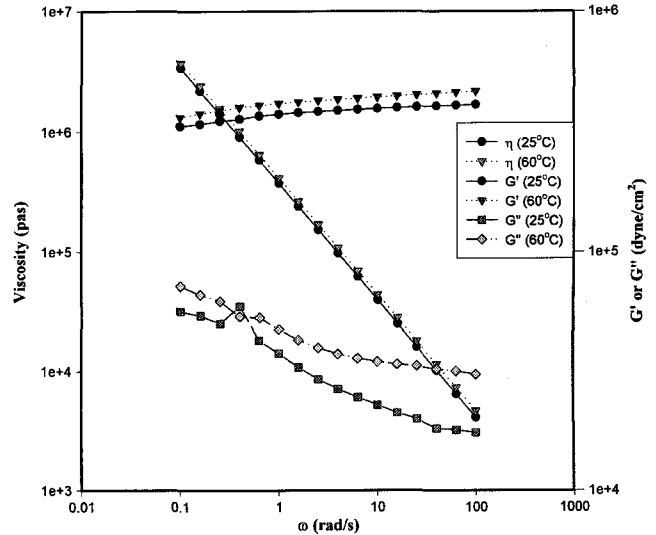


Figure 7—Viscoelastic properties of 25% poloxamer 407 solution depending on the frequency.

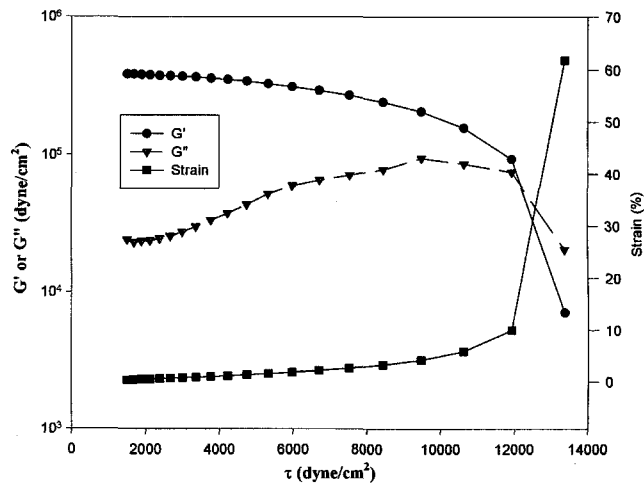


Figure 6—Storage modulus, loss modulus and strain of 25% poloxamer 407 solution depending on the shear stress.

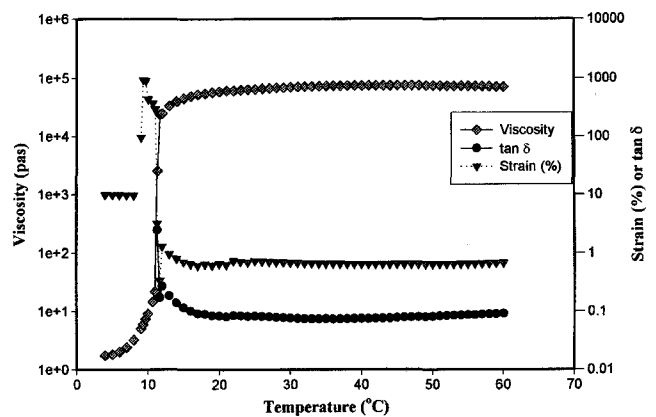


Figure 8—Viscoelastic properties of 25% poloxamer 407 solution depending on the temperature.

a measure of the energy reversibly stored and recovered per cycle in the system characterizing the elastic behavior of poloxamer. While loss modulus (G'') is a measure of irreversibly lost energy in each cycle characterizing the viscous behavior. Loss factor, $\tan\delta=G''/G'$, indicates the ratio between the viscous and elastic portion of the poloxamer and hence also the ratio between the amount of dissipated and stored energy during deformation for viscoelastic materials. In this result the values of storage modulus (G') stayed nearly constant, but with the increasing deformations they fell quickly. Such a behavior was attributed to the effect of strain amplitude on the structure of poloxamer gel. At higher deformations some changes of the arrangement may occur. The loss modulus values (G'') for the sample stayed nearly constant, but with the increasing defor-

mations they increase and fell quickly. Viscoelastic behaviors were determined as a function of frequency as shown Figure 7. It is observed that poloxamer 407 gels are viscoelastic fluids, having G' larger than G'' , that is their elastic components are larger than their viscous components.¹⁵⁾ It is also observed that G' does not change with ω , while G'' decreases with ω . Also, G' slightly increased with the increase in temperature. In the whole frequency range, elastic behavior was predominant for the poloxamer gels. A plateau in G' was characteristics of a gel state. In the gel state the storage modulus is independent of the frequency of the oscillations.¹⁶⁾

Figure 8 shows the temperature dependency on the viscoelastic properties of poloxamer 407 solution. In this figure the abrupt change at 12°C means the sol-gel transition of poloxamer 407.

Conclusion

The change of the rheological properties of poloxamer 407 depending on the temperature and concentration of poloxamer 407 was related with the gelation and dehydration process. From the viscoelastic properties, the sol-gel transition of poloxamer 407 was observed. And the gelation temperature was increased as the concentration of PEG 4000 increased.

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