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COMMUNICATION

Thermorheologic Properties of Aqueous Solutions and Gels of Poloxamer 407

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ABSTRACT

A rheological study of poloxamer 407 aqueous solution of 10–25% (w/w) concentrations was carried out at temperatures ranging from 27°C to 45°C and at various shear rates. An exponential relationship was found between viscosity and temperature, with curve slopes dependant upon poloxamer concentration. The viscosity of 25% poloxamer 407 aqueous solution showed a Newtonian fluid at 4°C and linearly increased on increasing temperature. The viscosity of 25% poloxamer 407 aqueous solution was sharply increased at about 12°C and maintained highly constant. During such a desolvation process, the closer approach of polymer chains, which gave rise to an increase in the number of interactions among the chains, gave an increase in the solution viscosity with temperature. The gelling concentration was examined using an interfacial tensiometer. The results showed that the first inflection point appeared at the 0.003% (w/w) concentration and the second point appeared at the 17.5% (w/w) concentration. It implied that poloxamer solutions formed monomolecular micelles at low concentration; as the concentration was increased, multimolecular aggregates were formed.

INTRODUCTION

Poloxamer 407 is a nontoxic poly(oxyethylene/oxypropylene/oxyethylene) (PEO/PPO/PEO) tri-block copolymer with a weight average molecular weight of 11,500. It contains 70% hydrophilic ethylene oxide units and 30% hydrophobic propylene oxide units. Concentrated aqueous solutions (20–30% w/w) of this polymer have been reported to show a dramatic increase in viscosity when heated from 4°C to room or body temperature. As a result of this reverse thermal gelation, the administered solution containing drug turns into a gel

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and renders slow release characteristics to the drug delivery system. This interesting characteristic has been exploited for the development of drug delivery systems (1–3).

The present study was undertaken to characterize the rheological properties of poloxamer 407 aqueous solutions for the basic study of gel development.

MATERIALS AND METHODS

Materials

Poloxamer 407 and 188 were received from BASF (Germany). Distilled water was used for the formulations.

Preparation of Aqueous-Based Poloxamer Gels

The cold technique was used for all formulas (1). Poloxamers were added into water at about 5°C and gently stirred. The solution was left overnight in a refrigerator to effect complete polymer desolvation.

Measurement of Viscosity

Rheological studies were performed with poloxamer 407 solutions thermostated at temperatures ranging from 4°C to 60°C, using a parallel plate rheometer (Rheometrics Rhios v4.3.2). The diameter of the plate was 40.0 mm and the gap between the sample and the plate was 1.778 mm.

Measurement of Interfacial Tension

To determine the gelation concentration, interfacial tension was measured at 4°C using an interfacial tensiometer (KRUSS K8, Germany) at various concentrations (0–25% w/v) of the poloxamer 407 or 188 solutions.

RESULTS AND DISCUSSION

Viscosity of the Solutions of Poloxamer 407

It has been known that poloxamer exists in the solution state at refrigerator temperature and in the gel state on warming to room temperature. Thus, the rheological properties of poloxamer solutions according to temperature were studied. The change of the viscosity according to the concentration of poloxamer and temperature was observed at a constant shear rate (Fig. 1). As the temperature and/or poloxamer concentration increased, the viscosity increased in the 15, 20, and 25% solution of poloxamer. However, the viscosity of the 10% solution of poloxamer remained relatively constant, regardless of increasing temperature. It was thought that the 10% solution of poloxamer did not form a gel.

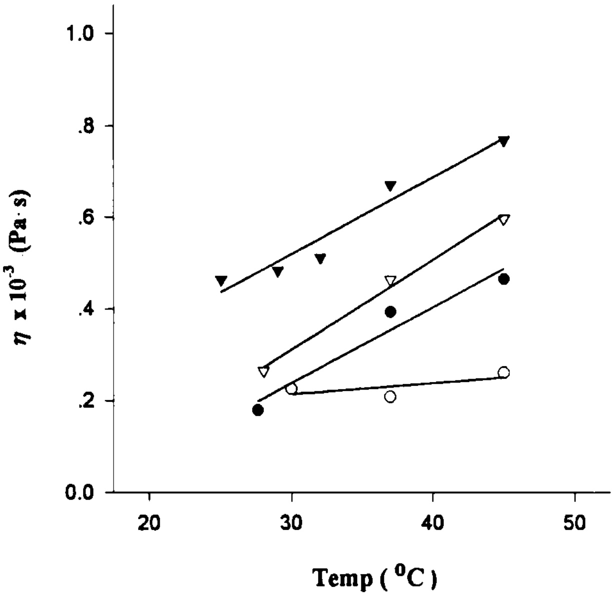

Figure 1. Viscosity of aqueous solution of poloxamer 407 according to concentration at various temperatures. ○, 10%; ●, 15%; ▽, 20%; ▼, 25%.

Rheological Behavior of 25% Aqueous Solutions of Poloxamer 407

These experiments were carried out to examine the phenomena that deform the 25% poloxamer solution above room temperature. The rheological property of poloxamer which exists in the solution state at 4°C was examined. Fig. 2 shows that the viscosity remained constant at 4°C in spite of the change of shear rate. It corresponded to Newtonian fluid, indicating no reduction in intermolecular interaction for shear thinning at the higher shear rate. On the other hand, it has been shown that the viscosity of this poloxamer gel decreased with increasing shear rate at 25°C (Fig. 3). It corresponded to pseudoplastic (shear thinning) fluid, indicat-

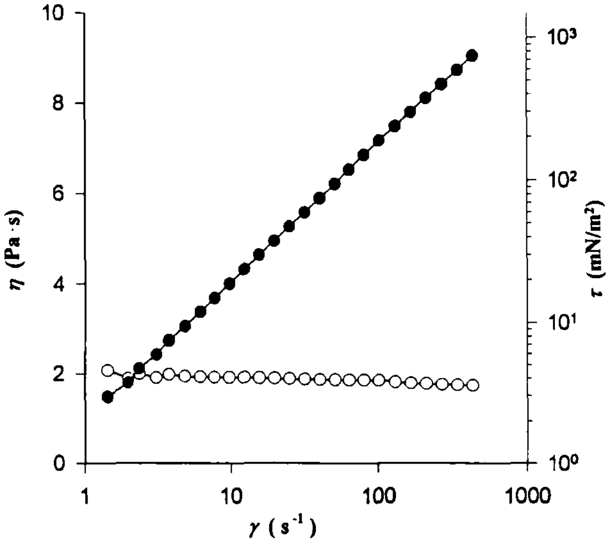

Figure 2. Viscosity and shear stress of 25% aqueous solution of poloxamer 407 as a function of shear rate at 4°C. ○, Viscosity (η); ● stress (τ).

ing some intermolecular interactions were present and responsible for shear thinning (4).

The viscosity was determined as the temperature was gradually increased from 4°C to 60°C. The viscosity of the poloxamer gel jumped sharply to the value of 2.3 × 10^4 Pa · sec at about 12°C and that of the poloxamer gel remained constant regardless of the increase of temperature (Fig. 4). Below 12°C, in the poloxamer 407 solution, the polymer chains exist as extended coils and are surrounded by a hydration layer (5). However, at the higher temperatures, the hydrogen bonding, especially between PPO units and water, becomes unstable, which leads to desolvation. The polymer chains therefore approach closer, which increases the number of interactions between polymer chains (4). It is believed that in polymer solutions, the various interactions between polymer chains regarded as localized junctions are responsible for an increase in viscosity and exhibiting of non-Newtonian flow (6). This was consistent with the result in concentrated solutions, whose behavior was observed to shift to pseudo-plastic and plastic when the temperature was increased (7)

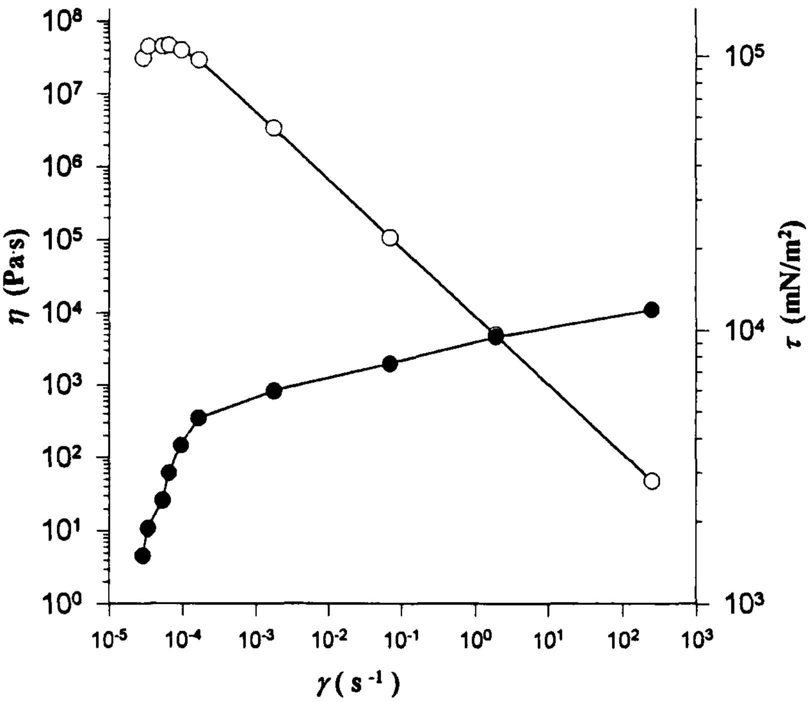

Figure 3. Viscosity and shear stress of 25% aqueous solution of poloxamer 407 as a function of shear rate at 25°C. ○, Viscosity (η); ● stress, (τ).

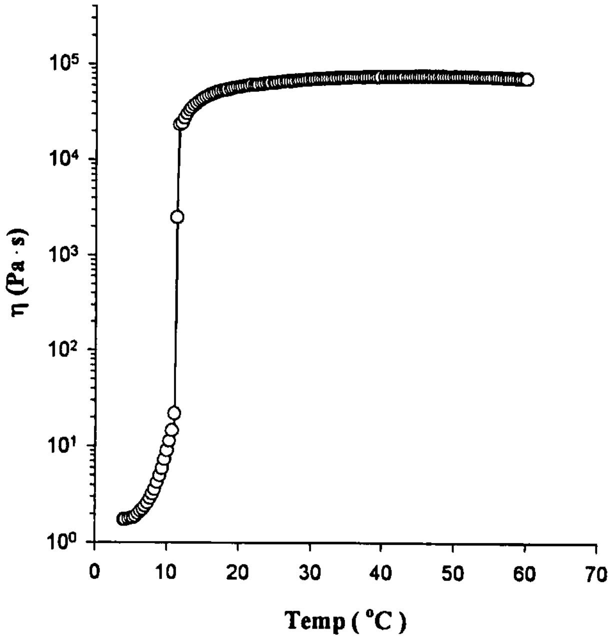

Figure 4. Viscosity of 25% aqueous solution of poloxamer 407 as a function of temperature.

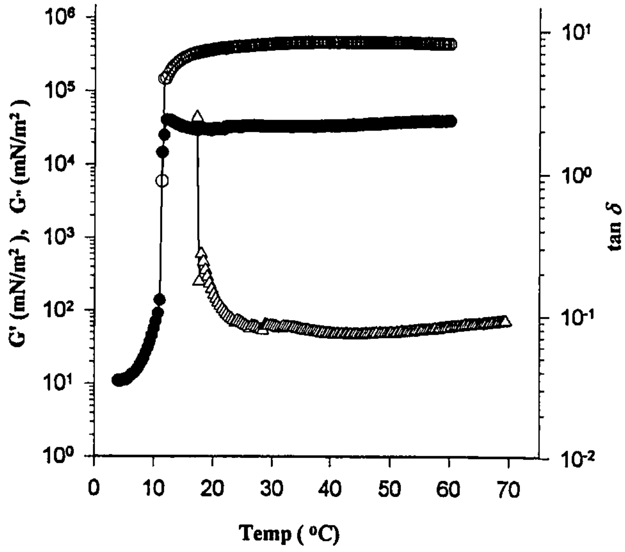

Figure 5. Rheology of 25% aqueous solution of poloxamer 407 as a function of temperature. ○, Storage modulus (G′); ●, loss modulus (G″); ∇, tan δ.

Fig. 5 shows that the shear loss modulus (*G*″) was larger than the storage modulus (*G*′) in the solution state, while *G*′ was larger than *G*″ in the gel state above the temperature. The storage modulus represents the characteristics of elasticity over the strain, while the loss modulus represents that of viscosity. Tan δ equals to the loss modulus divided by the storage modulus and is called loss tangent (8). Pluronic gels exhibit a reverse thermal gelation behavior which can be explained as a desolvation and swelling process of the copolymer to form cross-linked aggregates. In aqueous solution, pluronic molecules are surrounded by a hydration layer at low temperatures. But, when the temperature is raised, the hydrophilic chains of the copolymer are desolvated due to the breakage of the hydrogen bonds that had been established between the solvent and these chains. This phenomenon favors the hydrophobic interactions among the polyoxypropylene domains and leads to gel formation (9).

In summary, the polymer solution had the Newtonian behavior at 4°C (Fig. 2). As the shear rate increased, shear thinning phenomena caused the viscosity to abruptly decrease at 25°C (Fig. 3). These phenomena were observed at the heterogeneous state such as paint and block copolymer (10). It was thought that the poloxamer solutions remained in a homogeneous state where POE-POP-POE chains were well dissolved at a relatively low temperature of 4°C, but in a heterogeneous state where phase separation occurred on warming to 25°C.

Surface Tension of Poloxamer Solutions

The surface tension–concentration profiles of the two kinds of poloxamers studied are shown in Fig. 6. There are two marked inflections in the surface tension curve at concentrations of 0.003 and 17.5% (w/w). This range of concentration is close to the critical micelle concentration (CMC) range of conventional alkyl polyoxyethylene ethers (11). However, it is doubtful whether the first inflection point is a CMC because light-scattering and ultracentrifugation studies (12,13) demonstrated in similar systems the absence of polymolecular micelles at low concentrations. The first inflection point was attributed to a conformational change in the copolymer molecule, which gives rise to

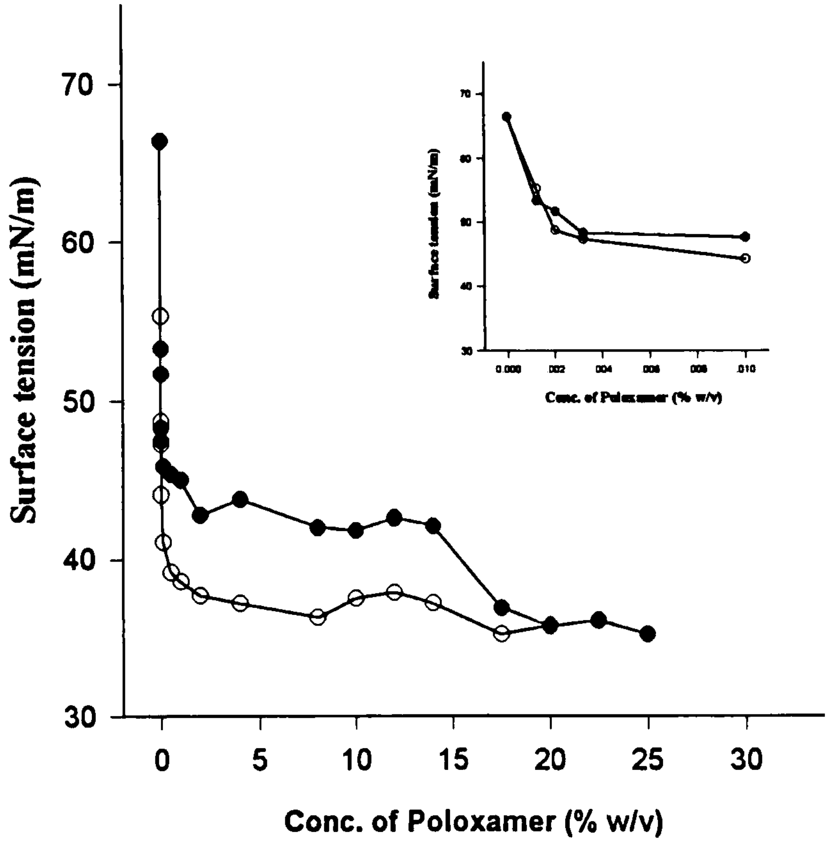

Figure 6. Interfacial tension at 4°C according to various poloxamers. ○, Poloxamer 407; ●, poloxamer 188.

a close-packed monomolecular unit with the hydrophobic chain coiled in its interior, shielded by the poly(oxyethylene) units. The second point of inflection was attributed to the formation of multimolecular aggregates more than to conventional micelles (14). It is suggested that such changes are a consequence of interactions between poly(oxyethylene) chains of adjacent micelles, which as a result of their dehydration, experience increased friction with a resulting tendency to form multimolecular units, leading eventually to gel formation (15).

ACKNOWLEDGMENTS

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