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Rheological behavior of poloxamer 407 aqueous solutions during sol-gel and dehydration processes

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Abstract

A rheological study of 25% poloxamer 407 aqueous solutions was undertaken during sol-gel and dehydration processes. Upon the sol-gel transition, the solution changed from a Newtonian to non-Newtonian fluid through the mechanism of desolvation. 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, was reflected by an increase in solution viscosity with temperature. In this study, three temperature regions, namely, the unimer, transition, and micelle regions originally derived from the light scattering technique, were also demonstrated. The boundary temperatures were 10°C between the unimer and transition regions and 18°C between the transition and micelle regions. Once the gel had been formed above the boundary temperature 18°C, the indices K and n remaining nearly constant, the gel structure was thought to remain unaltered with temperature until an excessively high temperature caused the destruction of the gel structure. At room temperature, the gel underwent a process of dehydration, the evaporation of water from the surface layer occurring first, and eventually dried to a solid. It was found that polyoxyethylene crystals precipitated in the gel during dehydration.

Key words: Poloxamer 407; Thermal gelation; Dehydration; Rheological properties; Power-law parameters; X-ray behavior

1. Introduction

Poloxamer 407 (trade name, Pluronic F-127), a non-toxic poly(oxyethylene/ oxypropylene/ oxyethylene) (PEO/PPO/PEO) tri-block copolymer with a weight-average molecular weight of 12500, contains 70% hydrophilic ethylene oxide units and 30% hydrophobic propylene oxide units. A 20–30% (w/w) aqueous solution of this compound is a clear liquid at refrigerator temperature. It forms a gel on warming to room temperature by undergoing a sol-gel transition. As a result of this reverse thermal gelation, the administered solution containing drug turns into a gel and renders slow release characteristics to the drug delivery system. The potential use of this compound as a drug delivery system has been the subject of a number of studies (Schmolka, 1972; Chen-Chow and Frank, 1981; Miyazaki et al., 1984).

It is believed that, on heating the poloxamer aqueous solution, three temperature regions, namely, the unimer, transition, and micelle regions, would respectively be reached (Zhou and

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Chu, 1988). In practice, no sharp critical micellization temperatures in the micellization of block copolymers are observed, since composition polydispersity frequently exists even in the case of a copolymer with a narrow distribution of molecular weight. As reported for poloxamers (Zhou and Chu, 1988), from the light scattering technique, the apparent hydrodynamic radius is approximately independent of temperature in the unimer and micelle regions but increases with temperature in the transition region. The driving force for those phase transitions is reported to be the increase in solution entropy through desolvation (Vadnere et al., 1984). With rise in temperature, the polymer chains may come closer and lead to an increase in the number of interactions among the chains. This increase in the number of interactions can be interpreted in terms of a corresponding increase in molecular weight and favors the formation of a gel (Boedtker and Doty, 1954). These three temperature regions may be associated with the rheological behavior during the process of sol-gel transition. The rheological properties, corresponding to the structure which is the arrangement of the polymer and water, would intrinsically be altered by dehydration. The present study was undertaken to characterize the rheological properties of poloxamer 407 aqueous solutions during gelation and dehydration processes.

2. Materials and methods

Poloxamer 407 supplied by BASF Wayndotte Co., Parsippany, was used without further processing in this study.

2.1. Methods

2.1.1. Sample preparation

25% poloxamer 407 aqueous solutions were prepared by the cold process (Schmolka, 1972; Chen-Chow and Frank, 1981). First, poloxamer 407 was placed in a small amount of distilled water with mild agitation at about 5°C. This polymer/water mixture (volume ratio around 1:3) was then kept refrigerated and properly sealed overnight. A concentrated polymer solution was obtained and diluted with water until the desired volume was reached. The solution was stored in a refrigerator until further use.

2.1.2. Rheology

A Rheometrics Fluids Rheometer (RFR 7800) was chosen for viscosimetric measurements. A cone-and-plate geometry was selected for all the measurements. The cone radius was 2.5 cm and the cone angle was 0.02 rad. In order to reduce the dehydration effect, viscosimetric measurement was started once the equilibrium temperature had been reached in the cone-and-plate gap.

2.1.3. Wide-angle X-ray diffraction

All samples were examined using a Siemens D 5000 diffractomer operated at 40 kV and 30 mA. Throughout the present work, nickel-filtered Cu-Kα radiation was used. A thin layer of liquid solution was placed on the zero-background plate made of quartz single crystal. The diffraction scans of the liquid solution and gel were recorded at around 5 and 23°C (room temperature), respectively. Then the scan of the gel was recorded after placing the gel in open air for 30 min at room temperature. It should be noted that the collection time for each step was only 1 s to reduce the dehydration effect, although a longer collection time is desirable for non-crystalline and low-crystallinity polymers.

3. Results and discussion

Typical viscosity vs shear rate curves of the poloxamer 407 aqueous solutions at various temperatures are shown in Fig. 1. A common power-law region for all curves can be found between 10 and 120 s^{-1} (Bird et al., 1977). In the power-law region, the formula $\eta = K \cdot \gamma^{n-1}$ was used, in which η is viscosity, γ the shear rate, and K and n are dimensionless quantities characteristic of each fluid. The calculated values of log K and n are listed in Table 1. A plot of the index n vs temperature is also shown in Fig. 2A. As can be seen, index n changes from 1 to 0.08 starting

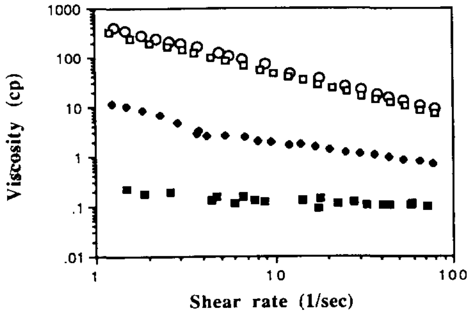

Fig. 1. Viscosity vs shear rate plots at 5°C (■), 16°C (◆), 20°C (□) and 60°C (○).

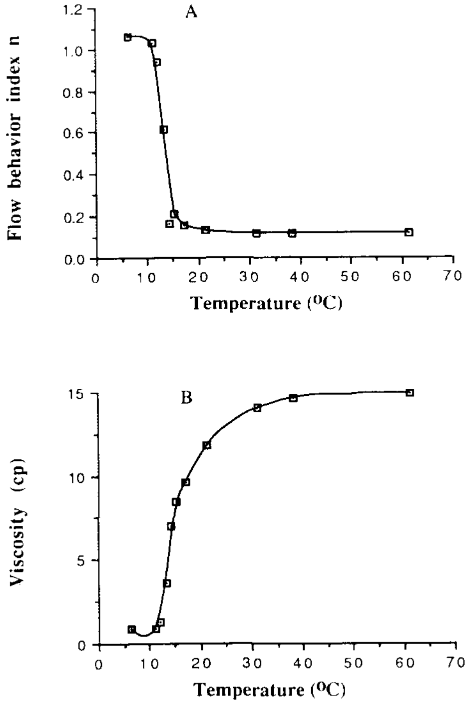

Fig. 2. (A) Flow behavior index n as a function of temperature; (B) viscosity at a shear rate of 50 s^{-1} as a function of temperature.

from 10°C, i.e., from Newtonian to non-Newtonian fluid.

The consistency index, K, is commonly temperature dependent, while the flow behavior index n is considered to be associated with the structure of the fluid (Bird et al., 1977). At temperatures between the ice point and 10°C, since index n is nearly equal to 1, it corresponds to Newtonian fluid, indicating no reduction in intermolecular interaction for shear thinning at the higher shear rate. Above 10°C, since index n is less than 1, it corresponds to pseudoplastic (shear thinning) fluid, indicating some intermolecular interactions were present and responsible for shear thinning. In the process of achieving a steady state at a given shear rate, the molecular interactions introduce a relatively longer relaxation time. However, the relaxation time must be sufficiently long for non-Newtonian flow to be observed. Consequently, the exact boundary between the unimer and transition regions may not be easy to define. In the present work, this boundary may be regarded as around 10°C.

Table 1
Calculated values of K and n and the measured viscosity at shear rate of 50 s^{-1} at various temperatures

Temperature (°C)	Log K	n	Viscosity (cp) (50 s^{-1})
5	−0.411	1.042	0.457
10	−0.397	1.033	0.456
11	0.123	0.906	0.919
12	1.219	0.582	3.227
13	2.285	0.135	6.537
14	2.304	0.177	8.049
16	2.457	0.122	9.232
20	2.587	0.099	11.382
30	2.693	0.083	13.647
37	2.713	0.082	14.235
60	2.721	0.082	14.500

Below 10°C, in the poloxamer 407 solution, the polymer chains exist as extended coils and are surrounded by a hydration layer (Rassing and Attwood, 1983). The molecular arrangement is more or less regular, which is the so-called unimer region (Zhou and Chu, 1988). However, at the higher temperatures, the hydrogen bonding especially between PPO units and water becomes unstable which leads to desolvation. Thus, the structure of the solution shows a more random pattern and contributes to the increase in solution entropy (Vadnere et al., 1984). The polymer chains therefore approach closer which increases the number of interactions between polymer chains. This is reflected by the increase in viscos-

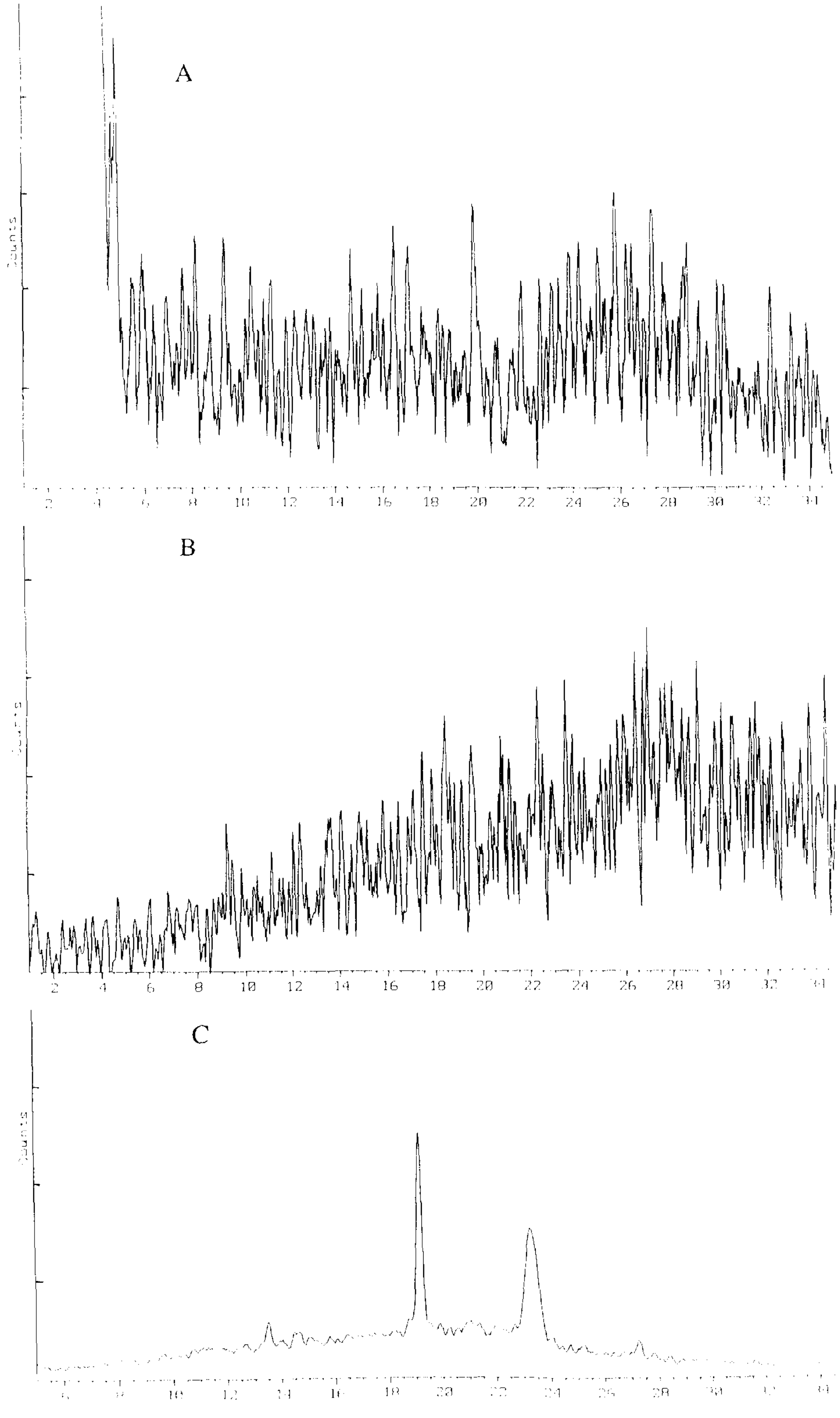

Fig. 3. Wide-angle X-ray diffraction patterns of: (A) the liquid solution; (B) the gel; (C) the precipitates in the gel.

ity, as shown in Fig. 2B. 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 (Lodge, 1956). A steady state is reached in which the rates of creation and dissociation of junctions become equal at a particular shear rate. In order to achieve the steady state, the greater number of interactions result in a longer relaxation time, which leads to an increase in index *n*. It can thus be suggested that, for the poloxamer 407 solution, as the temperature increases, resulting from the increase in the number of junctions, the index *n* decreases, as shown in Fig. 2A. From Fig. 2A, it is also observed that index *n* changes from 10°C until it reaches a constant value of 0.08 at 18°C. This 10–18°C temperature range corresponds to the transition region. Therefore, the boundary between the transition and micelle regions could be regarded as around 18°C.

As the temperature approaches 30°C, it is of interest to note that as the temperature increases the *n* values remain nearly constant and the log *K* values are very similar, in the vicinity of 0.08 and 2.71, respectively. This may reflect the fact that the molecular structure of the gel did not change with increasing temperature. Due to the limitations of the equipment, 60°C was the highest accessible temperature; as a consequence, the decrease in viscosity of the gel with temperature and break-down of the gel at higher temperatures were not observed in this work (Spancake et al., 1991).

The gel of index $n < 1$ is a pseudoplastic (shear thinning) fluid in nature; therefore, it is syringeable even in the gel state. This is an essential property for the practical use of poloxamer 407. As mentioned previously, since the number of junctions increases with temperature, the high-viscosity gel may be a form of network structure which is attributed to a greater number of junctions among the chains. There are two phases to be expected, namely, the micelle core phase (primarily formed by PPO units) and the aqueous phase (primarily formed by PEO units), following a micellization process (Zhou and Chu, 1988). The aqueous phase serves as the route for water soluble drug release, termed water channels in the work of Chen-Chow and Frank (1981).

Table 2
Calculated values of *K* and *n* as a function of time at room temperature

Time (min)	Log *K*	*n*
0	2.587	0.099
30	2.611	0.099
60	2.610	0.089
90	2.590	0.097
105	2.601	0.099
120	not available	

Provided that the gel is placed in open air at room temperature, water evaporates and the viscosity increases. However, a viscosity increase with time was not observed. As shown in Table 2, the indices *K* and *n* remain approximately constant with time, indicating that the gel was not subjected to structural change, until measurement could not conducted. This indicates that evaporation of water from the surface layer of the gel took place first and resulted in failure of the measurement. After a sufficiently long period of time, the gel dried to form a solid. This structural change will be mentioned later.

The rheological data prompted an investigation on X-ray behavior of poloxamer 407 solutions. The X-ray scattering patterns of the liquid solution and gel are shown in Fig. 3A and B. Since no sharp reflections were observed, the liquid solution and gel cannot be considered as liquid crystals, in contrast to the suggestion of Chen-Chow and Frank (1981) (Lenaerts et al., 1987). On the X-ray scattering patterns, diffusion maxima of 3.43 Å for the liquid solution and 3.24 Å for the gel can be found. Since these two diffusion maxima are considered to be derived from interferences between the neighboring polymer chains, the *d* spacings 3.43 and 3.24 Å are the average lateral distances between the chains. This result reveals that the chains draw closer in the gel than in the liquid solution. It can also be seen that the diffraction intensity increases towards small angles of scattering for the liquid solution but not for the gel, which corresponds to intramolecular interference, indicating a short-range ordering along the chain direction in the liquid solution (James, 1958). This may imply that the liquid solution appears to be more ordered than the gel. This phenomenon supports the presence of the increase in solution entropy during desolvation (or gelation).

Shortly after the gel was placed in open air at room temperature, a solid phase was precipitated in the gel. The diffraction scans of the precipitates are shown in Fig. 3C. From two prominent diffraction peaks at $\sin \theta/\lambda = 0.131$ and 0.108, the precipitates could be identified as PEO crystals based on the following unit cells: the monoclinic unit cell, $a = 8.05$ Å, $b = 13.04$ Å, c (fiber axis) $= 19.48$ Å, and $\beta = 125.4°$ (Takahashi and Tadokoro, 1973), and $a = 4.71$ Å, $b = 4.44$ Å, c (fiber axis) $= 7.12$ Å, $\alpha = 62.8°$, $\beta = 93.2°$, and $\gamma = 111.4°$ (Takahashi and Sumita, 1973). The detailed study of the crystal structures will be reported elsewhere (Tung, 1994). The result clearly indicates that the aqueous phase, namely, the water channels for water soluble drug release, underwent gradual reduction during dehydration and then disappeared finally when the gel turned into a solid.

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