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Thermorheologic Properties of Aqueous Solutions and Gels of Tetronic 1508

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The rheologic properties of aqueous solutions and gels of Tetronic 1508 were investigated as a function of polymer concentration and temperature utilizing rotational viscometry. Below the sol–gel transition temperature the polymer solutions were low in viscosity and exhibited Newtonian rheologic behavior even at concentrations of 20 and 25% (w/w). Upon sol–gel transition, the more concentrated polymer solutions underwent a dramatic four- to five-orders of magnitude increase in viscosity, resulting in the formation of a rigid gel structure. Above the sol–gel transition temperature, the gels displayed pseudoplastic and plastic rheologic properties and the viscosity of the gels remained at a relatively constant value over a wide temperature range. Eventually, the thermal energy of the system exceeded the bonding forces within the gel structure, resulting in a gel–sol transition which was marked by a dramatic decrease in the viscosity of the system. Above the gel–sol transition temperature, the system reverted to a Newtonian fluid with viscosities very similar to those found for the Tetronic 1508 solutions at temperatures below the sol–gel transition temperature. The thermodynamic implications of the gel–sol transition are discussed.

KEY WORDS: Tetronic 1508; thermal gelation; thermal gelling polymers.

INTRODUCTION

Poloxamines (Tetronics) are block copolymers synthesized by the sequential addition of propylene oxide and ethylene oxide to ethylenediamine (see Fig. 1) (1). Structurally, the Tetronics are very similar to the Pluronics, which are linear A–B–A block copolymers comprised of a hydrophobic polyoxypropylene segment sandwiched between two hydrophilic polyoxyethylene segments. As with the Pluronics, some of the members of the Tetronic series exhibit the unique property of thermal gelation, that is, aqueous solutions of the polymer (>18%, w/w) undergo a sol–gel transition upon increase in temperature (2).

The potential use of these polymers as a novel drug delivery system has been recognized by a number of researchers since aqueous solutions of the polymer can be formulated to exist in the fluid state at or near room temperature. The administered solution can subsequently undergo transition to the gel state at physiologic temperatures, rendering slow release characteristics to the delivery system. Some of the potential applications that have been investigated so far include topical delivery of silver lactate for the treatment of thermal burns (3), ophthalmic delivery of pilocarpine nitrate (4), rectal delivery of indomethacin (5), and subcutaneous delivery of recombinant interleukin 2 (6).

With the potential use of thermal gelling polymers as a drug delivery system, it is apparent that an understanding of the thermorheologic behavior of these polymers is essential. Unfortunately, there have been no published reports concerning the rheology of the Tetronic polymers and the literature on the thermorheologic properties of the Pluronic polymers is limited, especially at physiologic temperatures. Miller and Drabick (7) have reported viscosity values at 5 and 15°C of four members of the Pluronic series at concentrations ranging from 15 to 35%. Lenearts *et al.* (8) have performed rheologic studies on different concentrations of Pluronic F-127 at temperatures ranging from 5 to 30°C. They reported the viscosity of a 25% Pluronic F-127 gel at 30°C to be approximately 1.5×10^2 mPasec, while Chen-Chow and Frank (9) reported a value of 1×10^6 mPasec. The discrepancy in the two reported values can be explained by the fact that the viscosity values determined by Lenearts *et al.* were calculated at a rotational speed of 189.4 rpm, while Chen-Chow and Frank reported values at a rotational speed of 1 rpm.

Given the limited amount of rheologic data published for these thermal gelling polymers, the present report describes the complete thermorheologic profile of Tetronic 1508 at temperatures ranging from 15 to 70°C. It will be shown that the viscosity of these thermal gelling polymers does not continuously increase with temperature but, in fact, reaches a maximum value and eventually at higher temperatures undergoes a gel–sol transition which is accompanied by a dramatic decrease in viscosity. The thermodynamic implications of the gel–sol transition are discussed.

MATERIALS AND METHODS

Materials

Tetronic 1508 (gift from BASF Wyandotte), monsodium phosphate (Mallinckrodt), and disodium phosphate (Mallinckrodt) were used without any further purification.

Methods

Preparation of Tetronic 1508 Solutions

The polymer solutions, 10, 15, 20, and 25% (w/w), were prepared by the cold method (2), in which the appropriate amount of Tetronic 1508 was slowly added to a 0.1 *M* phosphate buffer (pH 7.0) with mild agitation using a magnetic stir bar. The polymer solutions were prepared in an ice bath and were then refrigerated overnight in order to produce a clear solution. The pH of the phosphate buffer was 7.00 at the gel–sol transition temperature. No attempt was made to measure the pH of the resulting polymer solutions or gels.

Rotational Viscometry Studies

The rheograms of the Tetronic 1508 polymer solutions were obtained using the Rheomat 115 rotational viscometer

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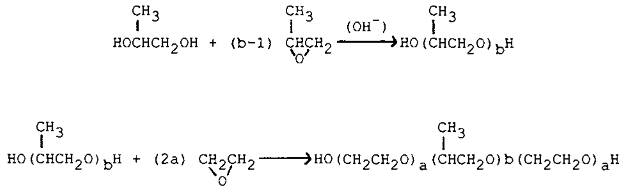

Fig. 1. Synthetic pathway for poloxamer block copolymers (from Ref. 1).

interfaced with the Rheoscan 100 microprocessor and Rheotherm 115 temperature control unit (Contraves, Zurich, Switzerland). Three different cup and bob measuring systems were used, depending on the viscosity of the polymer solution. For the 10% polymer solutions, the MS-0-115 double gap measuring system was used over the entire temperature range. This measuring system is a large-surface area double gap system capable of measuring viscosities as low as 1 mPasec. For the 15, 20, and 25% (w/w) polymer solutions, the DIN-145 measuring system was used for the solutions and the DIN-114 measuring system was used for the gels. The DIN-145 measuring system consists of a relatively large volume (125 ml) cup and a conicylindrical bob. Since the DIN-114 measuring system uses a conicylindrical bob with a much smaller surface area as compared to the DIN-145 measuring system, it allows for the measurement of high-viscosity gels. All of the measuring systems were encased in a thermostatically controlled jacketed assembly in order to maintain the sample temperature. The temperature of the system was controlled by a circulating water bath which can be monitored to within 0.1°C.

To obtain the rheograms, the appropriate measuring system was filled to the fill mark with the polymer solution and the sample was allowed to equilibrate to the experimental temperature. For the DIN-114 and MS-0-115 measuring systems, the sample temperature was assumed to be the same as the bath temperature since the sample volumes were small and in intimate contact with the jacketed wall of the cup. For the larger-volume DIN-145 measuring system, the temperature of the sample was monitored by a temperature probe which was located below the tip of the bob. Two different program cycles were used depending on the viscosity of the system. In the fluid state, the rheograms were obtained by increasing the bob rotation from 0 to 80 rpm and then reverting it to 0 rpm over a 4-min time span. In the gel state, the bob was rotated from 0 to 0.8 rpm and then back to 0 rpm over a 16-min time span. If the polymer solution did not exhibit Newtonian flow, the viscosity was calculated at a rotational speed of 0.025 rpm (rate of shear = 0.032 sec^{-1}). The rheologic data were digitized and sent to a X–Y plotter, which plotted rotational speed on the y axis and a value related to the shear stress on the x axis.

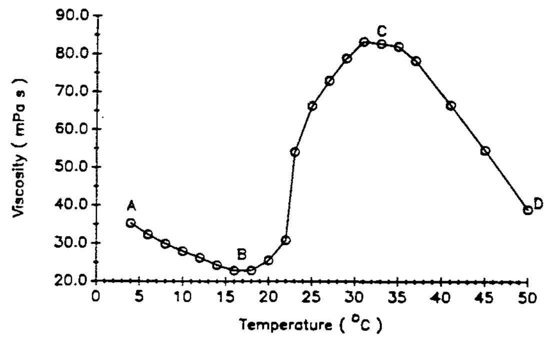

Fig. 3. Viscosity versus temperature profile of Tetronic 1508 at a 15% (w/w) concentration.

RESULTS AND DISCUSSION

The viscosity versus temperature profiles for the 10 and 15% Tetronic 1508 polymer solutions are shown in Figs. 2 and 3. It should be noted that these polymer solutions exhibited Newtonian rheologic behavior over the entire temperature range studied. Initially at low temperatures (region A → B), the polymer solutions exhibited a decrease in viscosity with an increase in temperature, a behavior typical of most Newtonian liquids and polymer solutions. Upon further increase in temperature (region B → C), the polymer solutions increased in viscosity, although the formation of a gel was not evident upon visual observation. This observed initial decrease in viscosity followed by an increase appears to be consistent with the results reported by Lenearts *et al.* (8) for the rheologic behavior of Pluronic F-127 solutions. As the temperature was further increased, however, the viscosity of the 10 and 15% Tetronic 1508 solutions reached a maximum value (point C) and then decreased with increasing temperature. Since previous rheologic studies have not been performed at higher temperatures, this decrease in viscosity has not been observed. This pattern of rheologic behavior will prove to be even more interesting for the 20 and 25% Tetronic 1508 systems which undergo the sol–gel transition.

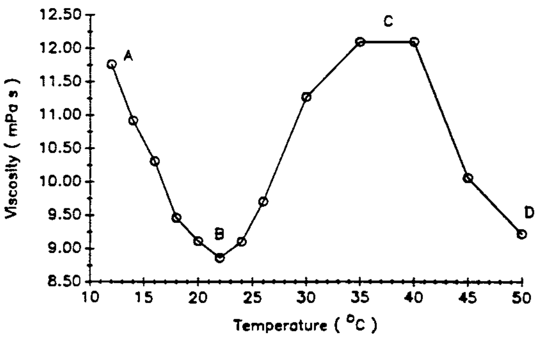

Fig. 2. Viscosity versus temperature profile of Tetronic 1508 at a 10% (w/w) concentration.

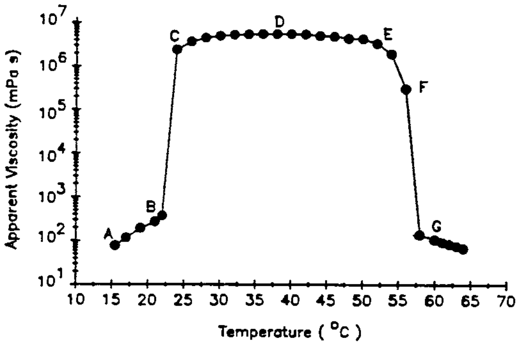

Fig. 4. Viscosity versus temperature profile of Tetronic 1508 at 20% (w/w) concentration.

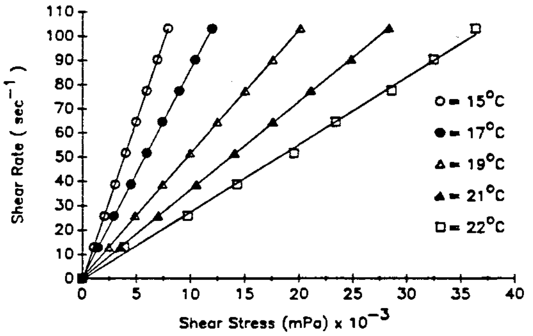

Fig. 5. Rheograms of Tetronic 1508 at 20% (w/w) concentration in the temperature range of 15 to 22°C.

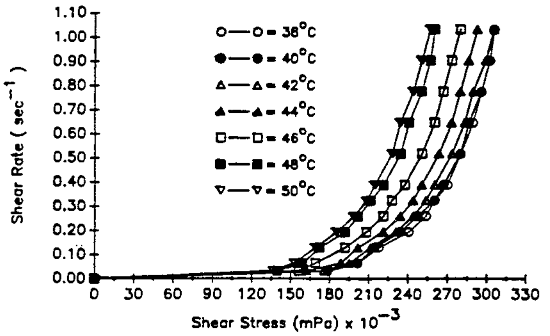

Fig. 7. Rheograms of Tetronic 1508 at 20% (w/w) concentration in the temperature range of 38 to 50°C.

Unlike the 10 and 15% polymer solutions which do not undergo the sol–gel transition, the 20 and 25% Tetronic 1508 solutions exhibit the property of thermal gelation in which the sol–gel transition is marked by a dramatic increase in viscosity and the formation of a rigid gel structure. Figure 4 represents the logarithm of the apparent viscosity versus temperature for the 20% Tetronic 1508 system. At low temperatures (region A → B), the polymer solutions are relatively low in viscosity and the rheograms indicate that these solutions are behaving as Newtonian fluids (Fig. 5), indicating minimal interactions between the polymer chains. As the temperature is increased through the sol–gel transition temperature, there is a dramatic four-orders of magnitude increase in viscosity (Fig. 4, region B → C) with simultaneous formation of a rigid gel structure. The polymer–polymer interactions that are responsible for the formation of the gel structure have been postulated to be due to hydrophobic interactions between the polyoxypropylene segments of the polymer (10). From the rheograms shown in Fig. 6, it is evident that the sol–gel transition is marked by a change from Newtonian to pseudoplastic and plastic flow behavior. However, the rheogram approximating the transition temperature (24°C) exhibits thixotropic behavior. This phenommenum is discussed shortly. The superimposable up and down curves on the rheograms indicate that the gels displayed very little thixotropy at the other temperatures shown in Fig. 6. Between point C and point D on the viscosity versus temperature profile, the viscosity of the gels continuously increased with temperature as evidenced by the shift in the rheograms to higher shear stress values (Fig. 6). After reaching a maximum viscosity at point D, the viscosity of the gels began to decrease (Fig. 7). Between point E and point F the hysteresis loops present in the rheograms indicated that the gels were becoming thixotropic in nature (Fig. 8). These rheograms are at, or near, the gel–sol transition. It is particularly noteworthy that thioxotropy is evident only at the sol–gel and gel–sol transition temperatures. The presence of thixotropy is indicative of time-dependent structural changes within the gel. Certainly, time-dependent changes may be anticipated when a solution becomes a gel, or vice versa, as the polymer is attempting to assume a new configuration while the viscosity, and thus the polymer mobility, is changing. The macroscopic rheological properties of the system at both transition temperatures are currently under investigation, particularly with respect to the time required to reach its equilibrium configuration.

Eventually, the thermal energy of the system exceeded the bonding forces within the gel structure and a gel–sol transition was observed. This transition was marked by a dramatic decrease in viscosity (Fig. 4, region F → G) resulting in the formation of a fluid phase with Newtonian rheologic properties (Fig. 9). From Fig. 10, it is apparent that the viscosity of the system as well as the sol–gel and gel–sol transition temperatures are very dependent upon the polymer concentration.

There are a number of significant practical and theoretical implications which stem from the experimental finding of these thermorheologic studies, especially since the literature on rheologic studies at temperatures greater than 30°C is limited. From a practical standpoint, if thermal gelling polymers were to be used as a delivery system, a knowledge of the viscosity as a function of temperature would be es-

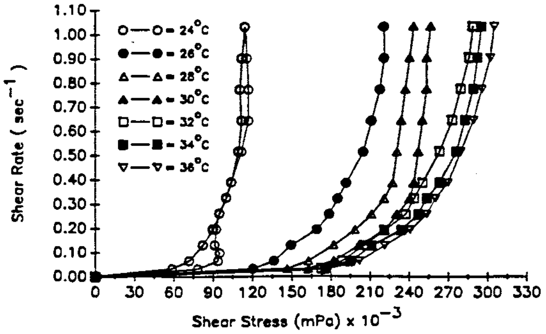

Fig. 6. Rheograms of Tetronic 1508 at 20% (w/w) concentration in the temperature range of 24 to 36°C.

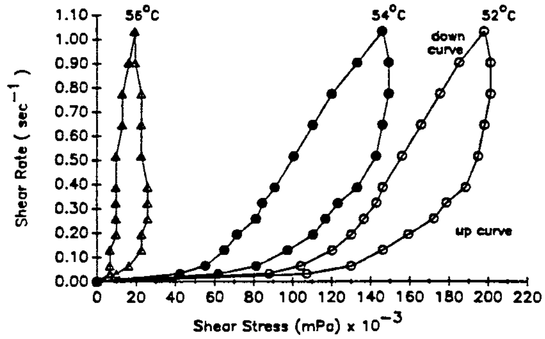

Fig. 8. Rheograms of Tetronic 1508 at 20% (w/w) concentration in the temperature range of 52 to 56°C indicating thixotropic behavior.

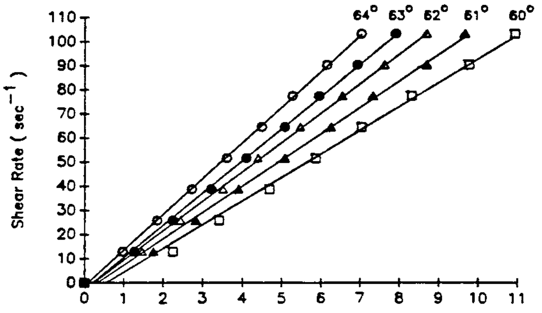

Fig. 9. Rheograms of Tetronic 1508 at 20% (w/w) concentration in the temperature range of 60 to 64°C.

sential in evaluating the physical integrity of the gel at physiologic temperatures. From Fig. 10, it is evident that the 20 and 25% Tetronic 1508 gels maintain a relatively constant viscosity over a wide temperature range, and therefore, slight changes in the physiologic temperature would not be expected to cause any dramatic changes in the physical integrity of the gel structure. In addition, the thermorheological information from Fig. 10 would also be very useful in selecting the proper manufacturing, packaging, and strorage conditions for a thermal gelling polymer delivery system.

One of the unique thermorheologic properties of the Tetronic polymer is that its solutions can exhibit the same viscosity ($\eta_1 = \eta_2$) at two very different temperatures ($T_1 < T_2$) as shown by the tie line in Fig. 11. Since the 20% Tetronic polymer solutions at T_1 and T_2 both exhibit Newtonian flow and have the same viscosity, the question arises whether or not these two systems are structurally the same. Figure 12 represents a plot of the logarithm of viscosity versus reciprocal temperature for the Newtonian 20% Tetronic 1508 polymer solutions at temperatures below the sol–gel transition temperature and above the gel–sol transition temperature. Utilizing the Arrhenius relationship [Eq. (1)], an "activation energy of flow" was determined using the data in Fig. 12.

$$\eta = Be^{-E_a/RT} \qquad (1)$$

$$\eta = Be^{E_a/RT} \qquad (2)$$

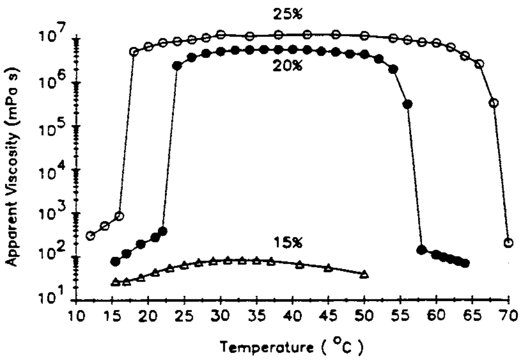

Fig. 10. Apparent viscosity (logarithmic scale) versus temperature (linear scale) profiles of Tetronic 1508 at three different concentrations 15, 20, and 25% (w/w).

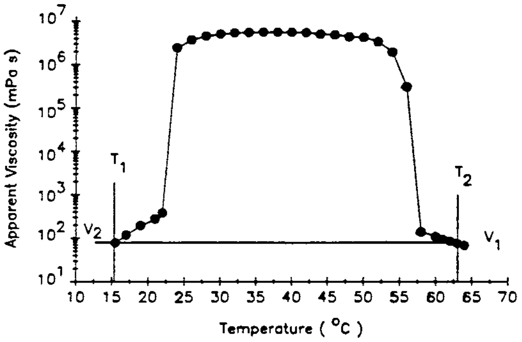

Fig. 11. A plot depicting similar apparent viscosities (V_1 and V_2) of 20% (w/w) Tetronic 1508 at two different temperatures.

Since the slopes of the two lines in Fig. 12 are obviously of opposite sign, Eq. (2) was used to calculate the activation energy of flow for the Tetronic 1508 solutions at low temperatures where the viscosity increased with temperature. It is apparent from Fig. 12 that at temperatures below the sol–gel transition temperature, the polymer solutions exhibit a greater increase in viscosity per degree increase in temperature as compared to those solutions which are at a temperature above the gel–sol transition temperature. This would tend to indicate that the polymer–polymer and polymer–solvent interactions are different at low temperatures compared to high temperatures even though the bulk viscosity is the same. It will be shown in our next report that while the macroscopic viscosity may be the same at two different temperatures, the viscosity within the "micro" environment is in fact different.

Another theoretical issue that needs to be addressed concerns the thermodynamics of the sol–gel and gel–sol transitions. Vadnere *et al.* (11) have investigated the thermodynamics associated with the sol–gel transition for some of the Pluronic polyols. In their study the assumption was made that at the transition temperature an equilibrium existed between the solution and the gel phases, which by definition necessitates that the change in free energy of the system (ΔG_1) must equal zero. Experimentally, they determined the change in enthalpy (ΔH_1) associated with the sol–gel transition utilizing solution calorimetry and by using the free energy, enthalpy, and entropy relationship derived by Eldridge and Ferry (12) to describe the concentration dependence of the gel–sol transition temperature for the gelation of gelatin, as shown in Eq. 3.

$$\ln C = \Delta H_{\text{gel}}/RT_{\text{trans}} + \text{constant} \qquad (3)$$

For Pluronic F-108, Vadnere *et al.* determined ΔH_1 to be approximately 6–8 kcal/mol. Since ΔG_1 was assumed to be equal to zero, the entropy change associated with the sol–gel transition (ΔS_1) must also be positive. Since the formation of a gel would be expected to result in a decrease in entropy, Vadnere *et al.* (11) postulated that the increase in entropy associated with the sol–gel transition may be due to the displacement of "bound" water from the hydrophobic segments of the polymer.

It appears reasonable that the sol–gel transition may in fact be entropically driven. Utilizing the relationship derived by Eldridge and Ferry (12), the change in enthalpy associated with the low-temperature sol–gel transition (ΔH_1) of Tetronic 1508 was determined to be approximately 7.26 kcal/

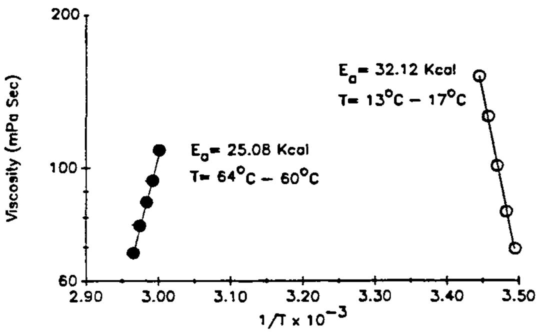

Fig. 12. Arrhenius-type plots of logarithm of apparent viscosity against reciprocal absolute temperature for the 20% (w/w) Tetronic 1508 system at the low and high range of the temperature scale.

mol, which appears to be consistent with the values reported by Vadnere *et al.* (11). At higher temperatures, however, the change in enthalpy associated with the gel–sol transition (ΔH_2) would be negative since the gel–sol transition temperature increases with polymer concentration (Fig. 13). If the assumption is made that the system is at equilibrium at the gel–sol transition temperature, then by definition the change in the entropy of the system (ΔS_2) must be negative. This finding is consistent with the postulate of Vadnere *et al.* (11). If sol-to-gel transition is accompanied by an increase in free water, then the reverse process is expected to cause a decrease in free water. Therefore in the sol state, water may be tightly bound to polymer chains causing hydration of the polymer, whereas in the gel state polymer chains may be undergoing hydrophobic association, thereby releasing the bound water and increasing the overall entropy of the system. Two points were used to calculate activation energies (Fig. 13) at each transition temperature, one representing the viscosity of the sol and the other the viscosity of the gel. As there is an abrupt change in viscosity associated with a small temperature change at the transition temperatures, it is not practical or necessary to obtain additional data points within this narrow temperature range.

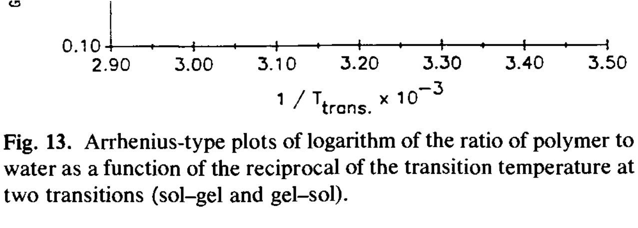

Fig. 13. Arrhenius-type plots of logarithm of the ratio of polymer to water as a function of the reciprocal of the transition temperature at two transitions (sol–gel and gel–sol).

The existence of the gel–sol transition has raised some interesting questions concerning the mechanism and thermodynamic driving force for the low temperature sol–gel transition and the high-temperature gel–sol transition of Tetronic 1508. At low temperatures, it appears that the sol–gel transition may be driven by an increase in the entropy of the system as postulated by Vadnere *et al.* (11). At higher temperatures, however, the negative enthalpic change may provide the thermodynamic driving force for the gel–sol transition. Also of interest is the microviscosity of the polymer solutions and gels. Gilbert *et al.* (13) have reported on the microviscosity of Pluronic F127 solutions and gels. The microviscosity of the Tetronic 1508 solutions and gels has been studied with respect to drug stability in the sol and gel phases and will be reported in a separate communication.

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