

# Kinetics of Sol-to-Gel Transition for Poloxamer Polyols

P. WANG and T. P. JOHNSTON\*

Department of Pharmaceutics, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612

## SYNOPSIS

Kinetics of gelation for aqueous solutions of poloxamers 407 and 288 were determined using pulse shearometry. The principle of this method for determining the shear modulus of a semisolid was based on generation of a torsional force that is transmitted through the poloxamer sample at discrete time intervals. Three distinct linear phases were observed for the log dynamic shear modulus ( $G'$ ) vs. time profiles as poloxamer 407 and 288 solutions of varying concentrations were allowed to passively warm at room temperature to a temperature exceeding the sol-to-gel transition temperature,  $T_m$ . The beginning of the second exponential phase coincided with the onset of the gelation process as determined by visual observation. Although gelation appeared visually to be complete at the beginning of the third exponential phase of the log  $G'$  vs. time profiles, this last exponential phase may indicate the rate of formation of the polymer network. A comparison of poloxamer 407 [30% (w/w);  $T_m = 10.9^\circ\text{C}$ ] and poloxamer 288 [37% (w/w);  $T_m = 11.1^\circ\text{C}$ ] would suggest that the concentration of poloxamer required to achieve approximately the same gelation temperature for poloxamers having a similar ratio of poly(oxypropylene):poly(oxyethylene) units decreases with increasing molecular weight of the poly(oxypropylene) hydrophobe contained in the copolymer. Results of these preliminary studies suggest that the gelation process was significantly ( $p < .05$ ) more rapid for poloxamer 407 at a 30% (w/w) concentration compared to a 30% (w/w) solution of poloxamer 288 when the poloxamer solutions were allowed to passively warm at room temperature. In addition, it appears that the rate of gelation for the poloxamer solutions studied was dependent on the rate of heat transfer through the polymer solution.

## INTRODUCTION

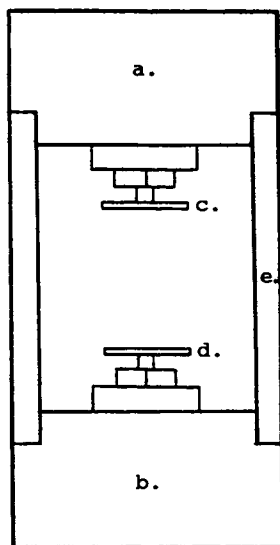
In recent years, there has been increasing interest in the determination of the shear modulus to physically characterize elastic liquids and gels. When a viscoelastic paste or gel is subjected to conditions of nonsteady shear, the value of the calculated shear modulus corresponds to the elastic component or the rigidity modulus of the viscoelastic material.<sup>1,2</sup> The value of the shear modulus indicates the extent of structuring in the gel system. The determination of the shear modulus is particularly well suited for systems that undergo a sol-to-gel transition due to some physical or chemical process. The rate of change in the value of the shear modulus affords an estimation of the rate at which the gelation process proceeds for a particular gel system.

The instrument known as a pulse shearometer, based originally upon a design by Van Olphen, has been used to study the elastic properties of a number of systems.<sup>3-6</sup> The pulse shearometer was used to characterize the elastic properties of bentonite clays,<sup>7</sup> concentrated colloidal suspensions consisting of polystyrene latices,<sup>8,9</sup> and clay dispersions.<sup>10</sup> This same instrument has also been widely used in the food industry to determine the shear modulus for food products known to undergo either thinning by shaking and stirring or thickening upon standing.<sup>2</sup> Other applications have included the evaluation of the effect of glucono-delta lactose (GDL) concentration on the cold settling of alginate-pectin gels,<sup>11</sup> as well as the effect of molecular mass and degree of branching on the gelation of amylose.<sup>12</sup> The advantage of using the pulse shearometer to determine the shear modulus of a gel system is that a small change in strain does not appreciably alter the gel formulation under investigation.

The present study was designed to determine the

\* To whom correspondence should be addressed.





**Figure 2** Schematic of the pulse shearometer measuring cell. Polypropylene housing containing the upper (a) and lower (b) piezoelectric crystals, (c) upper (receiving) disc, (d) lower (transmitting) disc, and (e) glass cylinder surrounding the sample compartment.

receiver disc (Fig. 2). When the shear wave arrives at the upper disc, it causes the disc to turn. The turning motion of the upper disc and the subsequent damping by the sample is immediately converted into an electrical potential that is followed on the color monitor. The resulting trace on the color monitor (Fig. 3) consists of a linear segment that occurs during transmission of the wave through the sample followed by a damped sine wave. The elapsed time from the initial movement of the lower disc to the peak of the first wave on the monitor is used to calculate the velocity of the shear wave through the polymer sample under investigation. The approximate frequency of the shear wave generated by the pulse shearometer is 200 Hz. It is the velocity of the shear wave that is measured by the pulse shearometer to yield the dynamic shear modulus,  $G'$ . The pulse shearometer in the present study was not equipped with a thermostat so a constant temperature environment could be maintained around the measuring cell containing the initially chilled solutions of poloxamers 407 and 238.

## Methods

### Vehicle Preparation

To determine the shear modulus of poloxamers 407 and 288 during the sol-to-gel transition, three matrices of each poloxamer at each concentration were prepared by the "cold-method"<sup>17</sup> using phosphate

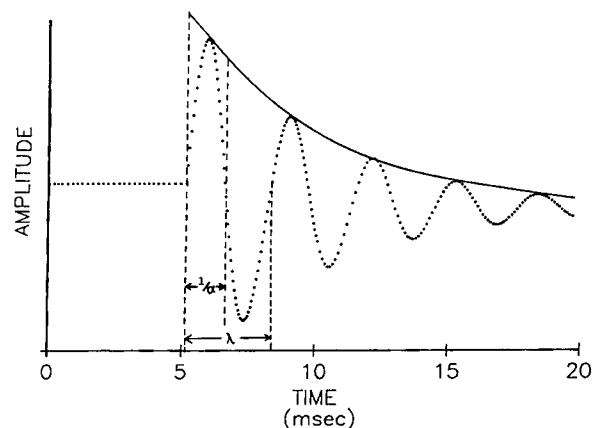
buffer as the solvent. Poloxamer 407 solutions were prepared by placing either 12 g [20% (w/w) matrices;  $n = 3$ ] or 18 g [30% (w/w) matrices;  $n = 3$ ] poloxamer 407 in tared 100-mL glass beakers. Phosphate buffer was then added to each set of three beakers to a final weight of 60 g. Poloxamer 288 solutions were prepared in a similar manner at a poloxamer concentration of 30% (w/w) [ $n = 3$ ] and 37% (w/w) [ $n = 3$ ]. All beakers were then placed in a refrigerator overnight to facilitate dissolution of the poloxamer vehicles in the phosphate buffer.

### Theoretical

The pulse shearometer was designed to measure the propagation velocity of a shear wave through a viscoelastic material that has been subjected to conditions of nonsteady shear.<sup>1,2</sup> The complex modulus that describes the response of the viscoelastic material undergoing nonsteady shear reflects the storage of energy and its dissipation in a frequency-dependent elasticity and viscosity, respectively.<sup>2</sup> The storage component of the complex modulus, i.e., the dynamic shear modulus,  $G'$ , is related to the velocity,  $V$ , of the shear wave and the density,  $\rho$ , of the sample through eq. (1)<sup>1</sup>;

$$G' = \rho \cdot V^2(1 - r^2)/(1 + r^2)^2, \quad (1)$$

where  $r = \alpha\lambda/2\pi$ ,  $\alpha$  being the attenuation coefficient of the amplitude of the wave and  $\lambda$  the wavelength (Fig. 3).<sup>2</sup> In the present study, the frequency of the wave generated in the pulse shearometer was approximately 200 Hz. The frequency varies slightly between 185–225 Hz as it is partly determined by



**Figure 3** Typical damped sinusoidal waveform observed on the oscilloscope following wave propagation through the poloxamer sample. ( $\alpha$ ), attenuation coefficient;  $\lambda$ , wavelength.

the crystal mounting, the seals, and the sample.<sup>8</sup> Small values of  $r$  are achieved when the stress relaxation time of the material is significantly longer than the period of the wave.<sup>18</sup> When the stress relaxation time of the material is significantly longer than the period of the wave on this time scale, the material behaves as an elastic solid (i.e., it has a Deborah number greater than 1) and the dynamic shear modulus,  $G'$ , is independent of frequency.<sup>18</sup> This results in eq. (2). In this case,  $G$  is the limiting value of the dynamic shear modulus that is reached at high frequency.<sup>18</sup>

$$G = \rho \cdot V^2. \quad (2)$$

Thus, the pulse shearometer determines the dynamic shear modulus at just a single frequency (approx. 200 Hz). To describe the rheological properties of the poloxamer system more completely would entail determination of both the dynamic elasticity and viscosity as a function of frequency. All dynamic shear moduli determined for the poloxamer 407 and 288 formulations in the present study were calculated using the approximate formula as given in eq. (2).

### Measurement of the Shear Modulus

Prior to the actual shear modulus measurements on the poloxamer 407 and 288 samples, the instrument was set to the "zero-separation" position. With the measuring cell empty, the upper receiver assembly unit was lowered carefully until the upper stainless steel disc was approximately 5 mm above the lower disc. The discs were then slowly moved together in discrete increments of separation distance via a height adjustment screw until a sinusoidal waveform was first observed on the monitor. The drive crystal was pulsed between each incremental adjustment of disc separation. The height adjustment screw was then used to position the disc so that the waveform just disappeared. This was defined as the zero-separation position of the two discs. The dial gauge height stop was adjusted until the gauge read zero with the measuring probe tip in contact with the center of the upper crystal assembly.

Prior to conducting shear modulus determinations on poloxamers 407 and 288, poloxamer samples were placed on ice until the solution obtained a temperature of 4°C. Either poloxamer 407 or 288 at a specified concentration (above) was then poured into the measuring cell of the pulse shearometer until the liquid level was slightly above the lower stainless steel disc. Since the initial temperature of

the poloxamer solutions was 4°C, the sample did not possess any structure. Lack of structure resulted in the disc separation being small to achieve a sinusoidal waveform on the color monitor. Once the sample was introduced into the pulse shearometer measuring cell, the upper receiver unit was lowered until the upper disc made contact with the liquid sample. Air bubbles that potentially might have been introduced between the discs were eliminated by pouring the liquid poloxamer solutions down the side of the cylindrical glass measuring cell. In addition, the upper disc was lowered with the entire pulse shearometer unit tilted to one side such that any microbubbles would rise in the solution and not become entrapped between the two discs.

The pulse shearometer was switched to the "TIMED-MODE" of operation (shear modulus determined as a function of time) and shear modulus measurements made at predetermined time intervals (every 2–3 min). The programmed TIMED-MODE of operation allowed up to 49 measurements of the shear modulus to be determined at a fixed time interval ranging from 30 sec–90 min. Thereafter, the experiment could be continued for an additional set of 49 measurements without disturbing the sample in the measuring cell.

As the sol-to-gel transition occurred for the poloxamer systems, the intensity and the velocity of the wave through the polymeric sample increased. This required adjustment of the gain control on the pulse shearometer's pulse generator interface unit throughout the course of the experiment. However, the level of sensitivity originally selected was kept constant throughout each series of measurements as suggested by the manufacturer.<sup>18</sup> Thus, the sample was allowed to form a gel (a more ordered three-dimensional network) while undergoing measurements of the shear modulus.

### Poloxamer Solution Temperature Studies

A parallel set of experiments ( $n = 3$ ), using an identical measuring cell to the one containing the parallel discs, were conducted simultaneously in which the temperature of the poloxamer 407 solutions [20 and 30% (w/w)] and poloxamer 288 solutions [30 and 37% (w/w)] were determined beginning with placement of the polymer solutions in the measuring cell (4°C) and continuing until all shear modulus measurements for a given poloxamer system had been obtained. This was accomplished by placement of a thermometer in the polymer solution adjacent to the inside wall of the glass measuring cell. Thus, the temperature of a given poloxamer solution was

obtained vs. time as the poloxamer formulations were allowed to passively warm at room temperature. In the present study, it was assumed that the mean value of the temperature obtained for a particular poloxamer solution/gel contained in the disc-free measuring cell vs. time was representative of the temperature of the poloxamer solution/gel simultaneously undergoing shear modulus measurements in the cell fitted with parallel discs.

## RESULTS

### Shear Modulus vs. Time Measurements

A plot of  $\log G'$  vs. time is shown in Figure 4 for poloxamers 407 and 288 as the poloxamer solutions passively warmed to room temperature after having been removed from an ice bath (0 min). It can be noted from Figure 4 that three distinct log-linear or exponential phases occur for each  $\log G'$  vs. time profile. The beginning of the second log-linear phase for each profile coincided with the point at which gelation of the system was first apparent from visual observation. The time at which gelation of the entire polymer matrix appeared complete from a visual inspection occurred at the beginning of the third log-linear phase (Fig. 4). Table I lists the mean values of the temperature that correspond to the time points at which the second and third log-linear phases began for each poloxamer matrix system evaluated as shown in Figure 4. As can be noted in Table I, the temperature range over which gelation was observed by visual examination to occur for a 30% (w/w) poloxamer 407 matrix was in close agreement to the temperature range of gelation observed for a 37% (w/w) poloxamer 288 matrix.

Since the value of the dynamic shear modulus for the poloxamer formulations increased exponentially with time following the onset of gelation, the second and third log-linear segments of the  $\log G'$  vs. time profiles can each be described by the first-order relationship in eq. (3), where  $k$  = a first-order rate constant.

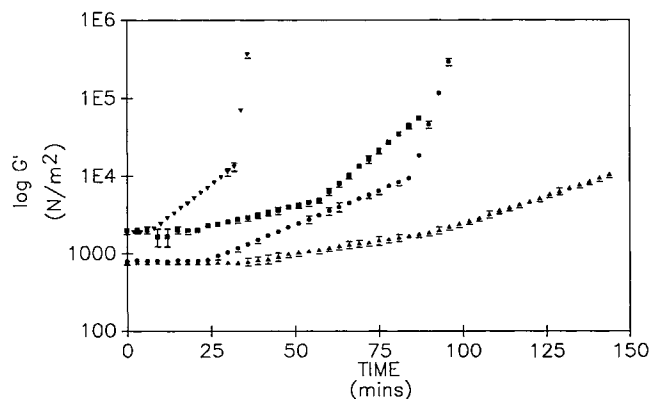
$$\frac{dG'}{dt} = kG' \quad (3)$$

Equation (3) may be integrated and expressed in exponential form as shown in Equation 4:

$$G'_2 = G'_1 \exp^{[k \cdot (t_2 - t_1)]}, \quad (4)$$

where  $G'_1$  = the dynamic shear modulus at time  $t_1$ ,  $G'_2$  = the dynamic shear modulus at time  $t_2$ , and  $k$  = the first-order rate constant obtained from the slope ( $2.303 \times$  slope) of the  $\log G'$  vs. time profile during the individual exponential phase. Equation (4) allows calculation of  $G'$  as a function of time during the sol-to-gel transition process for each concentration of the poloxamers evaluated by pulse shearometry. Since simultaneous parallel studies were conducted on the temperature of each poloxamer formulation vs. time, the  $G'$  may also be calculated as a function of temperature during the gelation process.

In the present study, the sol-to-gel transition process for each poloxamer was assumed to occur predominantly during the second log-linear phase of the  $\log G'$  vs. time profiles (Fig. 4) since this phase agreed well with visual observations noted for the apparent onset and conclusion of gelation. Using the second exponential phase of the  $\log G'$  vs. time



**Figure 4** Typical log shear modulus vs. time profiles for poloxamer 407 and 288 formulations. (●), 20% w/w poloxamer 407; (▼), 30% w/w poloxamer 407; (▲), 30% w/w poloxamer 288; (■), 37% w/w poloxamer 288.

**Table I Pertinent Parameters for the Sol-to-Gel Transition of Poloxamers 407 and 288**

Poloxamer Formulation	$G'$ (N/m <sup>2</sup> ) <sup>a</sup>	$t_{1/2 \text{ gel}}$ (min) <sup>b</sup>	$t_{1/2 \text{ final}}$ (min) <sup>c</sup>	$T_1$ [ $t_1$ ] (°C) [min] <sup>d</sup>	$T_2$ [ $t_2$ ] (°C) [min] <sup>e</sup>	$[\Delta H]/[\Delta t]$ 60 g (cal h <sup>-1</sup> g <sup>-1</sup> ) <sup>f</sup>
<b>P-407</b>						
20% (w/w)	801 ± 55 <sup>g</sup> ( <i>n</i> = 24)	17.1 ± 0.4 ( <i>n</i> = 3)	2.3 ± 0.1 ( <i>n</i> = 3)	18.9 ± 0.9 [22.0]	24.0 ± 1.1 [83.1]	11.9
30% (w/w)	1899 ± 46 ( <i>n</i> = 12)	9.1 ± 0.4 ( <i>n</i> = 3)	0.84 ± 0.02 ( <i>n</i> = 3)	7.8 ± 0.7 [6.78]	15.8 ± 0.6 [31.8]	33.2
<b>P-288</b>						
30% (w/w)	760 ± 5.5 <sup>h</sup> ( <i>n</i> = 12)	43.4 ± 3.5 <sup>h</sup> ( <i>n</i> = 3)	21.4 ± 0.05 <sup>h</sup> ( <i>n</i> = 3)	13.2 ± 0.8 [34.7]	20.6 ± 0.2 [89.0]	4.35
37% (w/w)	1920 ± 162 ( <i>n</i> = 8)	29.4 ± 0.5 ( <i>n</i> = 3)	8.6 ± 0.07 ( <i>n</i> = 3)	9.1 ± 0.5 [17.4]	15.0 ± 0.7 [56.4]	4.02

<sup>a</sup> Dynamic shear modulus calculated with eq. (2) for the first exponential phase of the log  $G'$  vs. time profiles shown in Figure 4.

<sup>b</sup> Half-time for the second exponential phase.

<sup>c</sup> Half-time for the third exponential phase.

<sup>d</sup> Mean temperature ( $T_1$ ) and approximate time [ $t_1$ ] at the onset of the second exponential phase.

<sup>e</sup> Mean temperature ( $T_2$ ) and approximate time [ $t_2$ ] at the onset of the third exponential phase.

<sup>f</sup> Estimate of the rate of heat supplied to the polymer solution during the second exponential phase.

<sup>g</sup> Mean value ± standard deviation of the mean value.

<sup>h</sup> Mean value significantly different ( $p < 0.05$ ) than the corresponding value for 30% (w/w) poloxamer 407 using Student's  $t$ -test.

profiles shown in Figure 4, the half-time of gelation,  $t_{1/2 \text{ gel}}$ , may be calculated for each poloxamer system evaluated. The mean values for the  $t_{1/2 \text{ gel}}$  are listed in Table I for each poloxamer formulation. Similarly, the half-times associated with the third log-linear phase,  $t_{1/2 \text{ final}}$ , of each log  $G'$  vs. time profile may be calculated for each concentration of the poloxamers tested (Table I).

For a given concentration of either poloxamer 407 or 288, the mean values of the half-times calculated for the third log-linear segment of the log  $G'$  vs time profiles are less than the mean values of the half-times calculated for the second log-linear phase (Table I). In addition, for a given poloxamer, the value of the mean half-time calculated for either the second or third log-linear phase decreases with increasing concentration of the poloxamer. As noted in Table I, the mean values for the  $t_{1/2 \text{ gel}}$  and  $t_{1/2 \text{ final}}$  for the 30% (w/w) poloxamer 288 matrices were each significantly longer ( $p < .05$ ) when compared to the mean values for the  $t_{1/2 \text{ gel}}$  and  $t_{1/2 \text{ final}}$  for the 30% (w/w) poloxamer 407 matrices, respectively.

For both poloxamers 407 and 288, the mean value of the dynamic shear modulus determined by pulse shearometry for the less-concentrated poloxamer solution was approximately 60% less than the mean value of  $G'$  for the more concentrated solution (Table I). However, as indicated in Table I, the mean value of  $G'$  for the 30% (w/w) poloxamer 288 solutions

was significantly less ( $p < .05$ ) than the mean value of  $G'$  determined for the 30% (w/w) poloxamer 407 solutions.

### Polymer Solution Temperature Studies

In the present study, the 20% (w/w) and 30% (w/w) poloxamer 407 matrices had obtained a temperature of 21.5 and 10.9°C at approximately 38 and 10 min, respectively, following removal from the ice bath (data not shown). Poloxamer 288 matrices [30% (w/w)] obtained the gel transition temperature of 19.2°C at approximately 77 min after the poloxamer solution, initially at 4°C, had been allowed to passively warm at room temperature (data not shown). At 10, 38, and 77 min, the mean values of the experimentally determined  $G'$  for the 30% (w/w) poloxamer 407, 20% (w/w) poloxamer 407, and 30% (w/w) poloxamer 288 formulations, respectively, fell within the second exponential phase of the observed triexponential log  $G'$  vs. time profiles (Fig. 4).

Based on visual observations in the present study, the temperature at which gelation appeared to begin for the 37% (w/w) poloxamer 288 solutions was 11.1°C. The average time required for the 37% (w/w) poloxamer 288 solutions, initially at 4°C, to reach 11.1°C was 35.3 min ± 1.2. As shown in Figure 4 for the 37% (w/w) poloxamer 288 formulation, 35.3 min falls within the time interval comprising

the second log-linear phase of the log  $G'$  vs. time profile.

### Rate of Poloxamer Gelation

The experimental findings in the present investigation seem to suggest that the rate of heat transfer through the polymer solutions was paramount in controlling the kinetics of poloxamer gelation or network formation.<sup>19</sup> If the assumption is made that the rate of heat transfer through the polymer solution controls the rate of gelation, then the gelation process can be described by ordinary conductive heat transfer processes. Since the cylindrical measuring cell was oriented in a vertical position and the polymer solution, when warmed above  $T_m$ , was a semi-solid in which free movement was hindered, natural convection of the polymer solution was unlikely. Thus, the Grashof number,  $N_{Gr}$ , was not calculated for the different polymer solutions.

The rate of heat transfer,  $q$ , through each polymer solution may be estimated by calculating an approximate value of the overall heat transfer coefficient,  $U$ . For the pulse shearometer used in the present study, heat is assumed to be transferred from the surrounding air to the glass wall of the measuring cell, through the glass wall, and, finally, to the polymer solution in contact with the inside surface of the measuring cell. The overall heat transfer coefficient may be estimated using eq. (5)<sup>20-22</sup>;

$$U = \frac{1}{1/h_1 + l_2/k_2 + 1/h_3}, \quad (5)$$

where  $h_1$  is the heat transfer coefficient between the surrounding ambient air and the glass measuring cell,  $l_2$  is the thickness of the glass wall of the measuring cell,  $k_2$  is the thermal conductivity of glass, and  $h_3$  is the heat transfer coefficient between the inner glass wall of the measuring cell and the polymer solution. Assuming values for the heat transfer coefficients  $h_1$  and  $h_3$  of  $0.5 \text{ Btu ft}^{-2} \text{ h}^{-1} \text{ }^\circ\text{F}^{-1}$  and  $500 \text{ Btu ft}^{-2} \text{ h}^{-1} \text{ }^\circ\text{F}^{-1}$ , respectively,<sup>20</sup> and  $k_2 = 0.4 \text{ Btu ft}^{-1} \text{ h}^{-1} \text{ }^\circ\text{F}^{-1}$ ,<sup>20</sup> an estimate of the overall rate of heat transfer may be made using eq. (6):

$$q = \frac{T_o - T_i}{1/h_1 + l_2/k_2 + 1/h_3}, \quad (6)$$

where  $q$  is the rate of heat flow from the air surrounding the measuring cell to the polymer solution inside,  $T_o$  is the temperature of the air outside the measuring cell ( $75.2^\circ\text{F}$ ),  $T_i$  is the initial temperature

of the polymer solution ( $39.2^\circ\text{F}$ ), and  $h_1$ ,  $l_2$ ,  $k_2$ , and  $h_3$  are as defined in eq. (5). For the value of the heat transfer coefficient from the inside surface of the glass wall to the polymer solution, namely,  $h_3$ , the assumption was made that the value of  $h_3$  for the polymer solution would be similar to that of water being heated<sup>20</sup> since the polymer solutions were approximately 65–80% water by weight. Substitution of these values into eq. (6) results in an overall value for  $q = 12.7 \text{ Btu ft}^{-2} \text{ h}^{-1}$ . Normalizing for the surface area of the measuring cell in contact with the ambient air, the estimate for the overall rate of heat transfer to the polymer solution adjacent to the inside wall of the measuring cell was  $10.9 \text{ cal. min}^{-1}$ .

The estimate of  $10.9 \text{ cal. min}^{-1}$  for the rate of heat flow to the polymer solution was then used to calculate the cumulative quantity of heat transferred through the glass wall to the polymer solution at the time points that corresponded with the start of the second and third exponential phases (Table I). Thus, it was possible to estimate the rate at which heat was supplied to the polymer solution by dividing the quantity of heat transferred to the polymer solution during the second exponential phase by the duration (min) of the second exponential phase. Values corresponding to the rate of heat flow through the polymer solution/g solution analyzed are listed in Table I. A more rigorous approach to the determination of the rate of heat flow through the polymer solution as both a function of distance from the inner surface of the glass cylinder and time is possible by modification of existing solutions to equations described in Crank.<sup>23</sup> However, no attempt was made in the present investigation to solve for the temperature gradient in the polymer solution as a function of both distance and time because the temperature was not measured at any other distance from the inner surface of the cell wall during the gelation process.

### DISCUSSION

The pulse shearometer is ideal for the study of polymeric systems that undergo gelation. In the case of polymers such as poloxamers 407 and 288, which exhibit reverse thermal gelation properties, poloxamer solutions at reduced temperature ( $4^\circ\text{C}$ ) may be poured directly into the measuring cell of the instrument and the shear modulus followed ( $G'$  vs. time) as the polymer solution is allowed to continually warm. The pulse shearometer is also useful for measuring the rate of gelation of polymers that do not display reverse thermal gelling properties. As an

example, the development of rigidity of a 5% (w/w) gelatin solution was investigated using this instrument by pouring the warm gelatin solution (40°C) into the measuring cell and determining the dynamic shear modulus vs. time when the solution had cooled.<sup>2</sup>

Wu,<sup>13</sup> using differential scanning calorimetry and viscometry, reported the temperature at which gelation occurs for a 20 and 30% (w/w) poloxamer 407 solution to be 21.5 and 10.9°C, respectively. In addition, it was reported<sup>13</sup> that the sol-to-gel transition temperature for a 30% (w/w) solution of poloxamer 288 was 19.2°C. The gel transition temperature for a 37% (w/w) poloxamer 288 solution can be estimated from the work of Vadnere et al.<sup>24</sup> to be approximately 11.9°C. Thus, based on the observation that the time of the apparent onset of gelation for each poloxamer concentration tested fell within the time range describing the second exponential phase of the triexponential  $\log G'$  vs. time profiles, it would suggest that this segment of the profiles represents the physical aggregation of the polymer chains (sol-to-gel transition). Presumably, a more ordered, three-dimensional structured state or network (gel) was forming during this time period. A slight tap on the side of the glass measuring cell of the pulse shearometer following the sol-to-gel process set into action the resonant vibrations of the gelled system that are characteristic of these "ringing" gels following complete transition from the liquid state to the semisolid gel state.

The longer time required for completion of the sol-to-gel process observed with poloxamer 288 [hydrophilic-lipophilic balance (HLB) = 28] may potentially result from its greater aqueous solubility compared to poloxamer 407 (HLB = 22).<sup>17</sup> The latter has an average molecular weight of 12,500 with 70% of the block copolymer consisting of hydrophilic poly(oxyethylene) units, whereas poloxamer 288 has an average molecular weight of 13,000 with an additional 10% of poly(oxyethylene) units incorporated into the molecule. Presumably, the added degree of hydrophilicity associated with poloxamer 288 requires a greater concentration of poloxamer 288 in the aqueous buffer to obtain the critical density of crosslinked polymer chains required for initiation of the aggregation or network formation process. Vadnere et al.<sup>24</sup> reported that the concentration required to achieve the same gelation temperature for poloxamers having a fixed ratio of poly(oxypropylene):poly(oxyethylene) units decreases with increasing molecular weight of the poly(oxypropylene) hydrophobe. Our results confirm the findings of Vadnere et al.<sup>24</sup> since poloxamer 407, which con-

tains 10% more poly(oxypropylene) units in the copolymer than poloxamer 288, required 7% by weight less polymer in solution to gel at approximately 11°C.

Based on thermodynamic studies, it has been previously reported<sup>24</sup> that the driving force for the thermal gelation of several poloxamers was due to a large entropic change. Vadnere et al.<sup>24</sup> suggested a model to account for their observed data that involved a local higher order of water molecules around the hydrophobic unit of the poloxamer in solution. It was suggested that as gelation of the poloxamers proceeded, the hydrophobic unit of the polymer molecules squeezed out the ordered water molecules into the bulk solution of lower order, resulting in an increase in entropy for the system.<sup>24</sup> Although factors such as the presence of additives and the number of poly(oxypropylene) units contained in the poloxamer have been reported<sup>24</sup> to influence the sol-to-gel transition of several poloxamers, the kinetics of the gelation process for poloxamers has not been evaluated.

The individual shear modulus vs. time profiles for the polymer solutions analyzed by pulse shearometry may be interpreted using the principles of heat transfer. Inspection of the  $\log G'$  vs. time profiles would suggest that in the initial exponential phase the polymer solution was warming, but remains ungelled. Thus, during this initial log-linear phase, little change in the shear modulus is detected by the pulse shearometer. After a sufficient quantity of heat has been transferred through the glass wall of the measuring cell to the layer of polymer solution immediately adjacent to the inside surface of the cylinder, the solution begins to gel. This time point was detected in the  $\log G'$  vs. time profile as the start of the second exponential phase and agreed closely with the time point at which the apparent onset of gelation was noted by visual inspection. However, the temperature at the time point where the apparent onset of gelation was detected both visually and by an increase in the value of the shear modulus was slightly below the previously reported  $T_m$  values for each poloxamer solution. As the gelled front moved toward the center of the cylindrical measuring cell, the shear modulus began to increase significantly. The log-linear increase in the value of the shear modulus with time in the second region of the profile probably reflects the rate of heat transfer through the polymer solution. Thus, it would appear that the rate of heat transfer through the polymer solution was the rate-controlling step in the polymer gelation process based on shear modulus measurements.<sup>19</sup> If the rate of aggregation of



the polymer chains were the rate-controlling step in the overall gelation process, then the entire polymer solution would have warmed above the  $T_m$  prior to the onset of an increase in the shear modulus.

The beginning of the third exponential phase potentially coincided with complete gelation of the polymer solution to the center of the cylinder. The sharp increase in the value of the shear modulus detected at the time point at which the third log-linear region began may indicate the rate of network formation in the polymer since the entire solution was now above  $T_m$  and heat transfer was no longer important. In addition, the steeper slope associated with the third exponential phase of the  $\log G'$  vs. time profiles as compared with the slope of the second exponential phase suggested that the rate of heat transfer was much slower than the rate of polymer network formation during the last exponential phase. Thus, the differences in the slopes of the third exponential phase may suggest differences in the rate of network formation for the individual polymer solutions once they have obtained a temperature greater than  $T_m$ .

### Implications for Sustained Release of Drugs

Determination of the rate of gelation for a poloxamer vehicle that exhibits "reverse-thermal" gelation properties is important were such a vehicle to be incorporated into an injectable, sustained-action formulation designed for extravascular administration. However, it was assumed that the rate of gelation for both poloxamers would be accelerated *in vivo* due to a constant 37°C environment rather than allowing the poloxamer formulations to passively warm to room temperature. Since the gelation process occurred at a faster rate with increasing concentration of poloxamer in the present study, it would imply that less drug incorporated in the more-concentrated poloxamer 407 and 288 matrices would be available for absorption immediately following parenteral (e.g., i.m.) injection. Presumably, the slower rate of gelation and less-rigid, three-dimensional gel structure formed with the less-concentrated poloxamer formulations would result in a potential "burst effect" of drug from the polymer matrix immediately following i.m. injection. In addition, lack of poloxamer matrix rigidity with the less-concentrated poloxamer solutions would cause the formulation to immediately spread out between the skeletal muscle fibers following i.m. injection. Theoretically, a greater area for drug absorption would be expected to result in an increase in the absorption rate of the drug following extravascular

administration.<sup>25,26</sup> Thus, formation of a sustained-action depot of drug may not be possible using the less-concentrated poloxamer formulations.

Based on this preliminary study of the gelation kinetics for poloxamers 407 and 288 using pulse shearometry, it would appear that poloxamer 407 is a more suitable vehicle than poloxamer 288 for incorporation into a sustained-action, parenteral formulation for extravascular administration. Examination of the mean values for the half-time of gelation,  $t_{1/2 \text{ gel}}$ , for poloxamer 407 in Table I would suggest that at a poloxamer 407 concentration of approximately 35–38% (w/w), formation of a drug/poloxamer 407 gel matrix would begin immediately following injection of a chilled formulation.

Future studies will be aimed at investigation of the rate of gelation of poloxamer 407 systems that contain biologically active macromolecules. In addition, the effect of several select pharmaceutically acceptable additives on the rate of gelation of various poloxamer 407/drug formulations will be investigated.

The authors are extremely grateful to Professor Michael J. Groves for his helpful discussions concerning viscoelasticity of polymeric systems and providing the pulse shearometer used for all shear modulus determinations. The authors also wish to acknowledge the technical assistance of Yao Hsueh and Sanda Hou with the shear modulus measurements.

### REFERENCES

1. F. T. Adler, W. M. Sawyer, and J. D. Ferry, *J. Appl. Phys.*, **20**, 1036–1041 (1949).
2. S. G. Ring and G. Stainsby, *J. Sci. Food Agric.*, **36**, 607–613 (1985).
3. J. W. Goodwin and A. M. Khidher, in *Colloid and Interface Science, Vol IV, Hydrosols and Rheology*, E. M. Kerker, Ed., 1976, pp. 592–547.
4. R. Buscall, P. D. A. Mills, and G. E. Yates, *Coll. Surf.*, **18**, 341–358 (1986).
5. J. W. Goodwin, T. Gregory, J. A. Miles, and B. C. H. Warren, *J. Coll. Interf. Sci.*, **97**, 488–495 (1984).
6. D. Brooks, J. Goodwin, C. Hjelm, L. Marshall, and C. Zukoski, *Coll. Surf.*, **18**, 293–312 (1986).
7. M. Van Olphen, *Clay Clay Miner.*, **4**, 204–224 (1956).
8. R. Buscall, J. W. Goodwin, M. W. Hawkins, and R. H. Ottewill, *J. Chem. Soc. Faraday Trans.*, **78**, 2873–2887 (1982).
9. R. Buscall, J. W. Goodwin, M. W. Hawkins, and R. H. Ottewill, *J. Chem. Soc. Faraday Trans. 1*, **78**, 2889–2899 (1982).
10. S. P. Golden, J. W. Goodwin, and A. D. Olal, *Trans. J. Br. Ceram. Soc.*, **81**, 84–87 (1982).

11. V. J. Morris and G. R. Chilvers, *J. Sci. Food Agric.*, **35**, 1370-1376 (1984).
12. H. S. Ellis and S. G. Ring, *Carbohydr. Polym.*, **5**, 201-213 (1983).
13. H. L. S. Wu, Ph.D. thesis, Univ. of Minnesota, Minneapolis, MN (1986).
14. K. A. Fults and T. P. Johnston, *J. Parenter. Sci. Tech.*, **44**, 58-65 (1990).
15. T. P. Johnston and S. C. Miller, *J. Parenter. Sci. Tech.*, **39**, 83-88 (1985).
16. T. P. Johnston and S. C. Miller, *J. Parenter. Sci. Tech.*, **43**, 279-286 (1989).
17. BASF Wyandotte Corp., Technical Data on Pluronic Polyols, Publication No. OS-796, Wyandotte, MI (1981).
18. Pen Kem Inc., Technical Data Bulletin on the "Rank Pulse Shearometer," Version 1.2, Bedford Hills, NY (1988).
19. M. Djabourov and J. Leblond, in *Reversible Polymeric Gels and Related Systems*, P. S. Russo, Ed., 191st Meeting of the American Chemical Society, Washington, DC, 1987, pp. 211-223.
20. W. L. McCabe, J. C. Smith, and P. Harriot, Principles of Heat Flow In Fluids, in *Unit Operations of Chemical Engineering*, W. L. McCabe, J. C. Smith, and P. Harriott, Eds., McGraw-Hill, New York, 1985, pp. 275-294.
21. E. L. Cussler, Heat Transfer, in *Diffusion: Mass Transfer In Fluid Systems*, E. L. Cussler, Ed., Cambridge University Press, New York, 1984, pp. 414-438.
22. H. W. Fowler, Heat Transfer, in *Cooper and Gunn's Tutorial Pharmacy*, S. J. Carter, Ed., Pitman Medical, New York, 1972, pp. 149-161.
23. J. Crank, in *The Mathematics of Diffusion*, Oxford University Press, London, 1956, pp. 67-70.
24. M. Vadrere, G. L. Amidon, S. Lindenbaum, and J. L. Haslam, *Int. J. Pharm.*, **22**, 207-218 (1984).
25. F. L. S. Tse and P. G. Welling, *J. Parenter. Drug Assoc.*, **34**, 409-421 (1980).
26. B. E. Ballard, *J. Pharm. Sci.*, **57**, 357-378 (1968).

Received April 30, 1990

Accepted November 27, 1990