Solute and Solvent Effects on the Thermorheological Properties of Poly(oxyethylene)–Poly(oxypropylene) Block Copolymers: Implications for Pharmaceutical Dosage Form Design

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ABSTRACT: Despite their widespread use as platforms for topical drug delivery systems, there is a relative lack of information concerning the thermorheological and viscoelastic properties of poloxamer systems and the effects of formulation components on these properties. To address this deficit, we examined the effects of the poloxamer concentration (25 and 35% w/w), molecular weight blend (poloxamer 407 and poloxamer 188), cosolvents (ethanol, propylene glycol, and glycerol), and presence of inorganic and organic electrolytes (sodium chloride and tetracaine hydrochloride, respectively) on these properties. The rheological properties were examined with a rheometer (4-cm-diameter, stainless steel, parallel-plate geometry) in either thermal sweep (0.5 Hz) or frequency sweep (0.01–1.0 Hz and 37°C) modes. Increasing the poloxamer concentration increased the elasticity [i.e., increased the storage modulus (G') and reduced the loss tangent (tan δ)] and reduced the sol–gel transition temperature (T_m) of all the formulations. Decreasing the ratio (407:188) increased T_m and reduced the elasticity of all the formulations. Increasing the concentration of ethanol, propylene glycol, or glycerol in the solvent reduced T_m. The presence of ethanol reduced G' and increased tan δ in a concentration-dependent fashion, whereas the viscoelastic properties of the poloxamers were more tolerant of glycerol (in particular) and propylene glycol. The elasticity of the formulations containing up to 10% glycerol and 5% propylene glycol was increased with respect to their aqueous counterparts. The presence of sodium chloride reduced T_m and, at lower concentrations (1 and 3%), increased G' and reduced tan δ for aqueous poloxamer systems. Conversely, the addition of a model therapeutic agent, tetracaine hydrochloride (5 and 7% w/w), significantly increased T_m and altered the viscoelastic character of the poloxamer system, notably reducing G' and increasing the loss modulus and tan δ. Alterations in the viscoelastic and thermorheological properties of aqueous poloxamer systems will have implications for their clinical performance. This study, therefore, has highlighted the need for the rational selection of components in the formulation of poloxamer systems as platforms for topical drug delivery. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 87: 1016–1026, 2003

Key words: transitions; viscoelastic properties; block copolymers

INTRODUCTION

The poloxamers are a series of nonionic ABA block copolymers of poly(oxyethylene) and poly(oxypropylene) of the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$.[1] The various interactions of poloxamers in aqueous solutions may be conveniently differentiated into three distinct physicochemical regions. First, as the concentration of the poloxamer increases in an aqueous solution, the existence of monomolecular micelles, in which the hydrophilic poly(oxyethylene) portions are coiled around the central hydrophobic poly(oxypropylene) unit, has been reported.[2,3] Second, at higher concentrations, poloxamers have been suggested to be present as multimolecular micelles as a result of both hydrophobic interactions between neighboring poloxamer chains and intermolecular and intramolecular hydrogen bonds between the ethereal oxygen atoms and the terminal, primary hydroxy groups.[4] Finally, above the critical micelle concentration, aqueous poloxamer systems may undergo a temperature-dependent sol–gel transition, in which the rheological properties of these systems are transformed from a low-viscosity colloidal solution to a gel.[4,5]

The presence of the sol–gel transition has generated an interest in the use of poloxamers for drug delivery applications. For example, Miyazaki et al.[6] described the use of poloxamer gels for the topical administration of anticancer agents, whereas Mohamed[7] employed such systems for the transdermal delivery of diclofenac. As a result of their excellent clarity at neutral pH, the applicability of poloxamers for the controlled delivery of therapeutic agents, such as pilocarpine and tropicamide, to the eye has been reported.[8,9]

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Furthermore, the exploitation of the sol–gel transition of these systems has been reported to enhance the efficiency of drug delivery systems, such as those for rectal administration,[10] for administration into the periodontal pocket,[11] and for the in situ production of a depot injection.[12]

It is accepted that the rheological properties of polymeric-based systems (e.g., poloxamers) are important determinants of their clinical and nonclinical performance.[13,14] Although a number of researchers have examined the flow properties of poloxamers with continuous shear rheometry, such as Miller and Drabik,[4] Lenaerts et al.,[5] Guzmán et al.,[15] Tung,[3] and Cho et al.,[16] this technique is destructive to the sample and yields little information concerning the structural properties, that is, the equilibrium rheological (viscoelastic) properties. The importance of structural rheological properties to the performance of topical drug delivery systems is well accepted, and the failure to examine these properties is an important oversight.[13,14] Currently, there is a relative paucity of information in the scientific literature concerning the structural rheological properties of poloxamer systems and, indeed, the effects of formulation components on such properties. Therefore, the aims of this study were to examine the equilibrium thermorheological properties of poloxamer systems and, specifically, to examine the effects of several physicochemical parameters, that is, the poloxamer molecular weight and solute and solvent composition, on these structural properties. In view of the potential relationships between these physicochemical parameters and the thermorheological properties of poloxamer systems, this study reports the use of a factorial experimental design to elucidate and quantify these relationships. This is the first report of the use of this statistical technique to gain an improved understanding of the rheological properties of poloxamer-based systems. The information derived from this study will be employed to improve the clinical and nonclinical efficacy of poloxamer-based drug delivery systems.

EXPERIMENTAL

Materials

Poloxamer 407 (molecular weight = 9840–14,600 g mol^{-1}) and poloxamer 188 (molecular weight = 7680–9510 g mol^{-1}) were donated by BASF (Ludwigshafen, Germany).

Tetracaine hydrochloride and sodium chloride were purchased from Sigma Chemical Co. (Poole, Dorset, England).

All other chemicals were purchased from BDH Laboratory Supplies (Poole, Dorset, England).

Manufacture of the poloxamer systems

All the poloxamer systems were prepared with the cold method as first described by Schmolka.[1] Initially, the required mass of the primary or binary solvent system, containing (where appropriate) dissolved sodium chloride (1–5% w/w) or tetracaine hydrochloride (3–7% w/w), was chilled to and maintained at circa 4°C throughout the manufacturing process. The required mass of the poloxamer or poloxamer blend was added to the chilled solvent with constant (mechanical) stirring until complete dissolution was achieved. All samples were stored at 4 ± 0.1°C until required and were tested within 72 h of their manufacture. A number of experimental variables were examined in this study:

- The effects of the molecular weight blend on the thermorheological and viscoelastic properties of poloxamer systems. Poloxamer systems were prepared containing poloxamer 407 and poloxamer 188 in the following proportions: 100/0, 90/10, 80/20, 70/30, 60/40, and 50/50. The total masses of the poloxamers were 25 and 35% (w/w), and the solvent system was deionized water.
- The effects of the mixed (binary) solvent systems on the thermorheological and viscoelastic properties of poloxamer systems. Poloxamer systems were prepared with water and ethanol, water and propylene glycol, or water and glycerol in the following proportions: 100/0, 95/5, 90/0, 85/15, 80/20, and 75/25% (w/w). In all cases, the total poloxamer content was 25% (w/w), and only the higher molecular weight polymer (poloxamer 407) was employed.
- The effects of the solutes on the viscoelastic properties of poloxamer systems. Aqueous poloxamer systems (25% w/w, poloxamer 407) were prepared with sodium chloride (1, 3, or 5% w/w) or tetracaine hydrochloride (1, 3, 5, or 7% w/w).

Oscillatory rheometry of the poloxamer systems

Oscillatory rheometry of the poloxamer systems was performed with a Carri-Med CSL^2-100 rheometer (TA Instruments, Leatherhead, Surrey, UK) with a 4-cm-diameter, stainless steel, parallel-plate geometry and a plate separation of 1 mm. The samples were carefully removed from their storage containers, applied to the lower plate of the rheometer, and allowed to equilibrate for at least 1 h before analysis. The linear viscoelastic region for all systems was initially investigated by a torque sweep from 0.1 to 100 Pa at frequencies of 0.01 and 1 Hz. In this frequency region, stress was directly proportional to strain, and the storage modulus (G') remained constant.[17] From the identified linear viscoelastic region, a constant strain of 1.5×10^{-3}

TABLE I
Effects of Poloxamer Blend Composition and Concentration on the Sol–Gel Transition of Aqueous Poloxamer Systems

Poloxamer concentration (% w/w)	Poloxamer blend composition (407:118)[a]	Mean (± standard deviation) T_m (°C)
25	100:0	16.68 ± 0.39
25	90:10	19.05 ± 0.57
25	80:20	31.33 ± 1.06
25	70:30	[b]
25	60:40	[b]
25	50:50	[b]
35	100:0	<5′[c]
35	90:10	7.57 ± 0.69
35	80:20	11.67 ± 0.63
35	70:30	24.08 ± 0.93
35	60:40	[b]
35	50:50	[b]

[a] Mass ratio of poloxamer 407 to poloxamer 188, as described in the Experimental section.
[b] No sharp sol–gel transition was observed.
[c] The sol-gel transition occurred below the minimum temperature employed in the analysis.

was chosen for all rheological measurements. Two distinct oscillatory rheological analyses were employed in this study: oscillatory thermorheological analysis and frequency sweep analysis. The former method was employed to identify the sol–gel transition temperature (T_m) and was involved in the application of a defined oscillatory frequency (0.5 Hz) over a range of sample temperatures (5–55°C). T_m was defined as the temperature at which a sharp increase in G' occurred.[18,19] In frequency sweep analysis, a range of oscillatory frequencies (0.01–1.0 Hz) was applied to each sample at a defined strain (1.5×10^{-3}) and at a selected temperature representing physiological conditions (37°C). In both methods, the calculation of viscoelastic parameters was performed with proprietary software (TA Instruments, Leatherhead, Surrey, England). In all cases, at least six replicate analyses were performed.

Statistical analysis

In this study, several different statistical analyses were performed. The effects of the molecular weight poloxamer blend (the ratio of poloxamer 407 to poloxamer 188) and concentration of the poloxamer or the effects of the cosolvent type (ethanol, propylene glycol, or glycerol) and concentration on both T_m and the viscoelastic properties [i.e., G', loss modulus (G''), and loss tangent (tan δ)] at three representative frequencies (0.1142, 0.5307, and 1.001 Hz) were statistically evaluated with a two-way analysis of variance (ANOVA). Furthermore, the effects of sodium chloride and a model therapeutic agent, tetracaine hydrochloride, on both T_m and the viscoelastic properties were statistically analyzed with a one-way ANOVA. When required, post hoc statistical comparisons of the means of individual groups were performed with Tukey's honestly significant difference test. In all analyses, $p < 0.05$ was accepted to denote significance.[14,17,20]

RESULTS

The effects of the poloxamer molecular weight and concentration on T_m of aqueous poloxamer systems are presented in Table I. For systems containing 25% (w/w) poloxamer, a sharp sol–gel transition was observed whenever the concentration of the higher molecular weight polymer was equal to or greater than 80%. The sol–gel temperature sequentially increased (significantly) as the proportion of the high molecular weight poloxamer (407) was reduced from 100 to 80% (w/w). For systems containing 25% (w/w) total poloxamer in which the proportion of poloxamer 407 was less than 80%, a sharp increase in G' was not observed, and T_m could not be identified. However, gradual increases in G' of these samples were observed with increasing temperature. For systems containing a total poloxamer content of 35% (w/w), a sharp sol–gel transition was observed in those containing 70, 80, or 90% (w/w) poloxamer 407. In the sample containing 100% (w/w) poloxamer 407, gelation occurred below 5°C. T_m increased significantly with sequential decreases in the proportion of poloxamer 407 between 100 and 70% (Table I). For samples containing less than 70% (w/w) poloxamer 407, a sharp increase in G' was not observed, and T_m could not be identified. However, gradual increases in G' of these samples were observed with increasing temperature. T_m's were significantly higher for samples containing a total poloxamer content of 25% (w/w) than

TABLE II
Effects of Vehicle Composition on the Sol-Gel Transition of Poloxamer (Poloxamer 407, 25% w/w) Systems

Solvent	Vehicle composition (cosolvent: water) as a percentage of the total formulation	Mean ± standard deviation T_m (°C)
Water	75	16.68 ± 0.39
Ethanol	5:70	14.30 ± 0.37
Ethanol	10:65	12.05 ± 0.44
Ethanol	15:60	11.00 ± 0.84
Ethanol	20:55	[a]
Ethanol	25:50	[a]
Propylene glycol	5:70	13.95 ± 0.54
Propylene glycol	10:65	10.53 ± 0.38
Propylene glycol	15:60	6.53 ± 0.46
Propylene glycol	20:55	<5[b]
Propylene glycol	25:50	<5[b]
Glycerol	5:70	13.17 ± 0.44
Glycerol	10:65	8.33 ± 0.46
Glycerol	15:60	5.48 ± 0.61
Glycerol	20:55	<5′[b]
Glycerol	25:50	<5′[b]

[a] No sharp sol–gel transition was observed.
[b] The sol–gel transition occurred below the minimum temperature employed in the analysis.

for the equivalent system with a total poloxamer content of 35% (w/w).

T_m's of systems containing 25% poloxamer 407 in mixed solvents of water and ethanol, water and propylene glycol, and water and glycerol are presented in Table II. A sharp sol–gel transition was observed in samples containing up to 15% ethanol, the temperature of which significantly decreased with each incremental increase in the ethanol content. For the sample containing 20% ethanol, the sol–gel transition was not sharp, occurring in the region of 25–30°C, and was superimposed on a gradually increasing G'. A sharp sol–gel transition was also observed in samples containing up to 15% propylene glycol. The temperature at which this transition occurred was significantly reduced with each incremental increase in the propylene glycol content. For samples containing 20 or 25% propylene glycol, T_m was reduced below 5°C, and samples existed in the gel state over the entire temperature range observed. Further increases in the propylene glycol content from 15 to 20% and from 20 to 25% significantly reduced G' of the gelled systems. Similarly, a sharp sol–gel transition was also observed for samples containing up to 15% glycerol, the magnitude of which significantly decreased with each sequential increase in the glycerol content. For samples containing 20 and 25% glycerol, T_m decreased below 5°C, and the samples existed in the gel state over the entire temperature range observed.

The effects of selected solutes on T_m values of aqueous poloxamer (407) systems (25% w/w) are presented in Table III. Increasing the concentration of sodium chloride sequentially from 0 to 1% and from 1 to 3% (w/w) significantly reduced T_m. Furthermore, in systems containing 5% (w/w) sodium chloride, T_m was reduced below 5°C, and the system existed in the gel state over the entire temperature range observed. Conversely, a sequential increase in the concentration of tetracaine hydrochloride from 3 to 7% (w/w) significantly increased T_m of the poloxamer system.

Interestingly, statistical interactions were observed between the concentration and molecular weight of the poloxamer and, in addition, between the type and concentration of the solvent. In the former, the effects of increasing the percentage of the low molecular weight poloxamer on T_m were greater when the total poloxamer content was 25% (w/w) than when 35% (w/w) of this polymer was present. In the latter case, the effects of the increasing concentration of the cosolvent on the lowering of T_m were dependent on the

TABLE III
Solute Effects on the Sol–Gel Transition of Aqueous Poloxamer (Poloxamer 407, 25% w/w) Systems

Solute	Mean ± standard deviation T_m (°C)
Control (water)	16.68 ± 0.39
Sodium chloride (1% w/w)	12.67 ± 0.37
Sodium chloride (3% w/w)	8.17 ± 0.67
Sodium chloride (5% w/w)	<5′[a]
Tetracaine hydrochloride (1% w/w)	16.03 ± 0.37
Tetracaine hydrochloride (3% w/w)	17.85 ± 0.49
Tetracaine hydrochloride (5% w/w)	21.48 ± 0.52
Tetracaine hydrochloride (7% w/w)	25.43 ± 1.07

[a] The Sol–gel transition occurred below the minimum temperature employed in the analysis.

nature of the cosolvent. The greatest effect was associated with glycerol, followed by propylene glycol and ethanol.

The effects of the molecular weight and polymer concentration on the viscoelastic properties of aqueous poloxamer systems are illustrated in Figure 1(a,b). Increasing the total concentration of the poloxamer significantly increased G' and G'' and reduced tan δ of the poloxamer systems over the observed oscillatory frequency range. Conversely, increasing the percentage of the low molecular weight poloxamer reduced G' and G'' and increased tan δ. Accordingly, the maximum and minimum G' values were recorded with the formulations containing 35% (w/w) poloxamer 407 and a blend of 15% (w/w) poloxamer 407 and 10% (w/w) poloxamer 188. The relationships between G' and the oscillatory frequency and between tan δ and the oscillatory frequency for all formulations tended toward a plateau after exposure to a defined frequency greater than around 0.15 Hz. These effects are illustrated in Figure 2(a,b). The observed magnitudes of (1) G' and G'' and (2) tan δ for all formulations were large and small, respectively, indicating that these systems possessed essentially elastic behavior. A statistical interaction was observed between the effects of the poloxamer concentration and molecular weight on the viscoelastic properties of the gelled systems. In this, the effects of the alteration of the molecular weight poloxamer blend on G', G'', and tan δ were proportionally greater for systems containing 25% (w/w) poloxamer than for those containing 35% (w/w) of this polymer.

The effects of the solvent type and composition on G' and tan δ for aqueous poloxamer (407) gels (25% w/w) are shown in Figure 3(a,b), respectively. Increasing the concentration of ethanol incrementally from 0 to 10% (w/w) did not significantly alter G' and G'' or tan δ of the gel systems. However, the introduction of 20 or 25% (w/w) ethanol significantly reduced

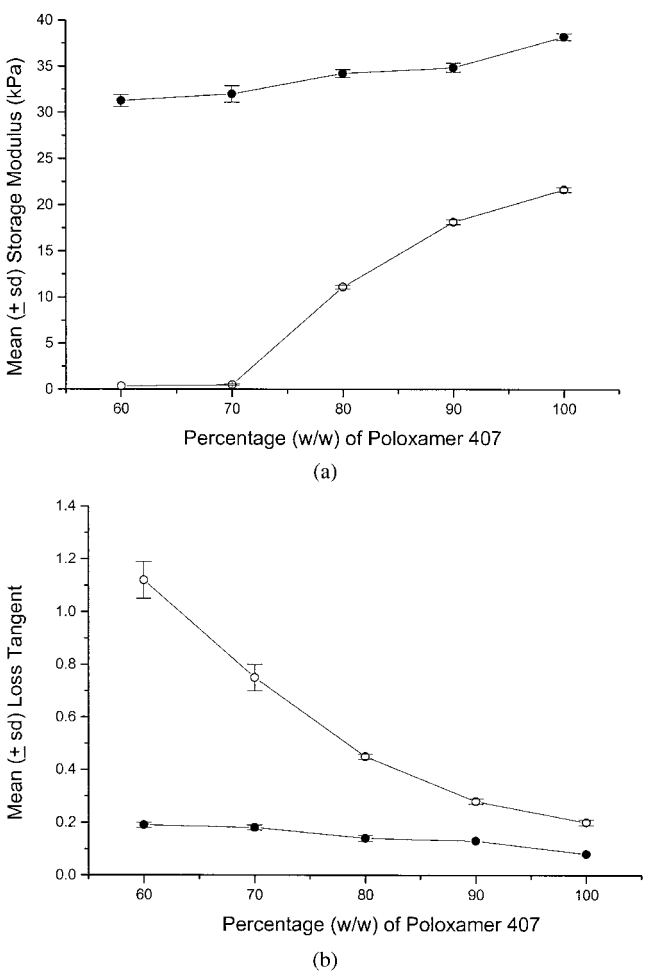


Figure 1 Effect of the molecular weight poloxamer blend on (a) G' and (b) tan δ for aqueous poloxamer formulations: (●) formulations containing 35% (w/w) total poloxamers and (○) formulations containing 25% (w/w) total poloxamers.

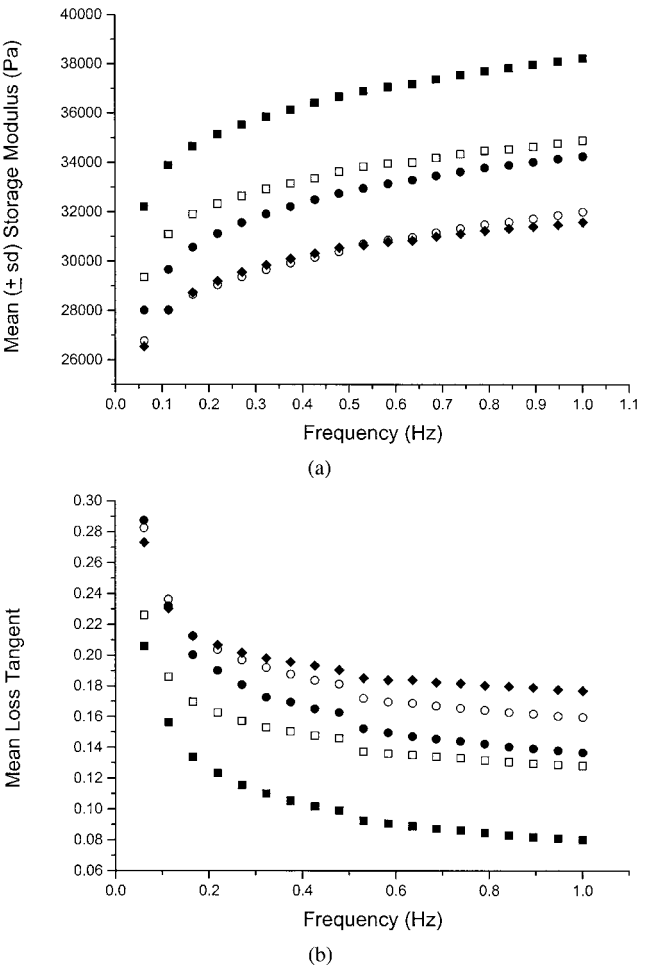
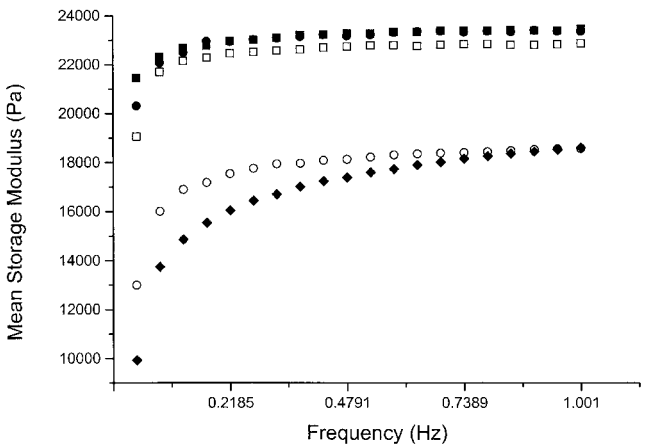


Figure 2 Effects of the oscillatory frequency on (a) G' and (b) tan δ for aqueous poloxamer gels (35% w/w) containing different ratios of poloxamer 407 and poloxamer 188: (■) 100:0, (□) 90:10, (●) 80:20, (○) 70:30, and (♦) 60:40. Error bars have been omitted for clarity; however, the coefficient of variation was less than 5% in all cases.

G' and G'' and increased tan δ of the poloxamer systems over the entire range of oscillatory frequencies. For propylene glycol [Fig. 4(a,b)], the incorporation of 5% of this cosolvent significantly increased G' and G'' and reduced tan δ, whereas the viscoelastic properties of systems that contained 10 and 15% of this diol were statistically similar to those exhibited by the aqueous control. In the presence of 20% propylene glycol, G' and G'' were significantly reduced and tan δ was significantly increased in comparison with the aqueous control. Similarly, the introduction of glycerol as a cosolvent significantly affected the resultant viscoelastic properties of the poloxamer system [Fig. 5(a,b)]. However, the nature of this effect was different from that previously observed for other cosolvents. Increasing the concentration of glycerol from 0 to 5% and from 5 to 10% significantly increased both G' and G'' and reduced tan δ. For example, at 1.001 Hz, G' and



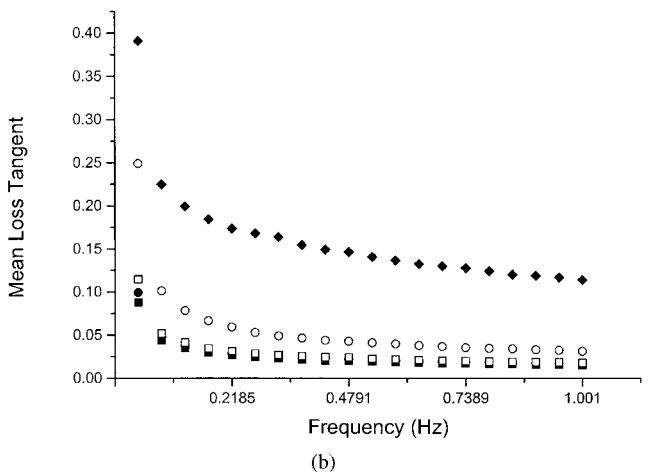
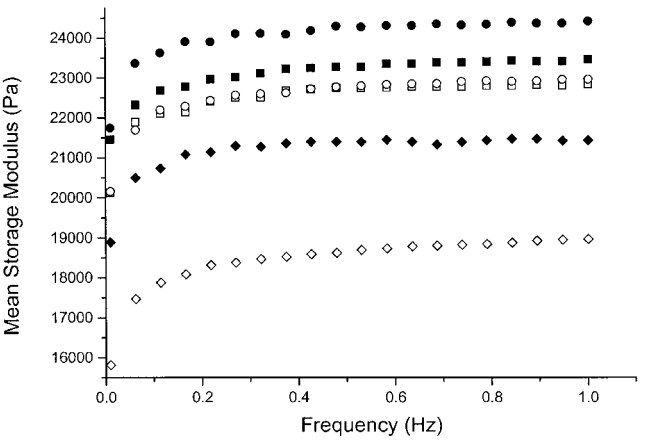


Figure 3 Effects of the oscillatory frequency on (a) G' and (b) tan δ for poloxamer 407 gels (25% w/w) containing different concentrations of ethanol: (■) 0, (●) 5, (□) 10, (○) 15, and (♦) 20%. Error bars have been omitted for clarity; however, the coefficient of variation was less than 6% in all cases.



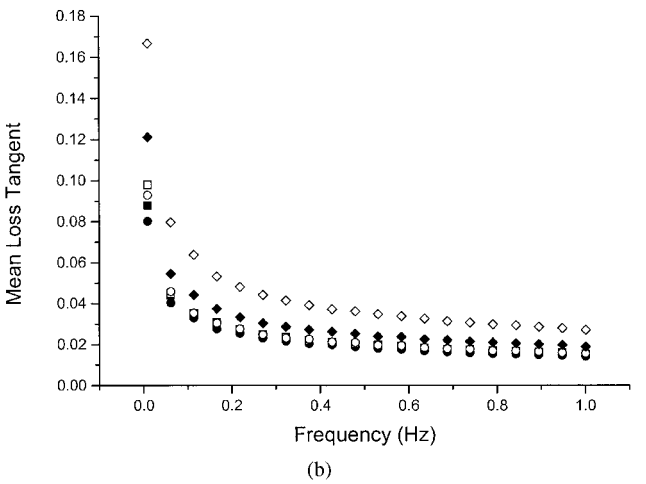


Figure 4 Effects of the oscillatory frequency on (a) G' and (b) tan δ for poloxamer 407 gels (25% w/w) containing different concentrations of propylene glycol: (■) 0, (●) 5, (□) 10, (○) 15, (♦) 20, and (◇) 25%. Error bars have been omitted for clarity; however, the coefficient of variation was less than 8% in all cases.

tan δ for aqueous poloxamer gel were 23.46 ± 0.26 kPa and 0.015 ± 0.001, respectively, whereas in the presence of 10% (w/w) glycerol, G' and tan δ were 27.88 ± 0.67 kPa and 0.010 ± 0.001, respectively. Conversely, in the presence of 15 and 20% (w/w) glycerol, G' and G'' were significantly lower and tan δ was significantly greater than the moduli of aqueous poloxamer gel systems devoid of this cosolvent. In comparison with the aqueous poloxamer system (G' = 23.46 ± 0.26 kPa and tan δ = 0.015 ± 0.001), G' and tan δ of the system containing 20% glycerol were 17.14 ± 0.32 kPa and 0.025 ± 0.001, respectively. The disparities in the effects of the three solvents on the viscoelastic properties of the poloxamer gels accounted for the observed statistical interactions observed between each cosolvent and concentration.

The effects of solutes on the viscoelastic properties of poloxamer gel systems are presented graphically in Figures 6 and 7(a,b). As may be observed, increasing

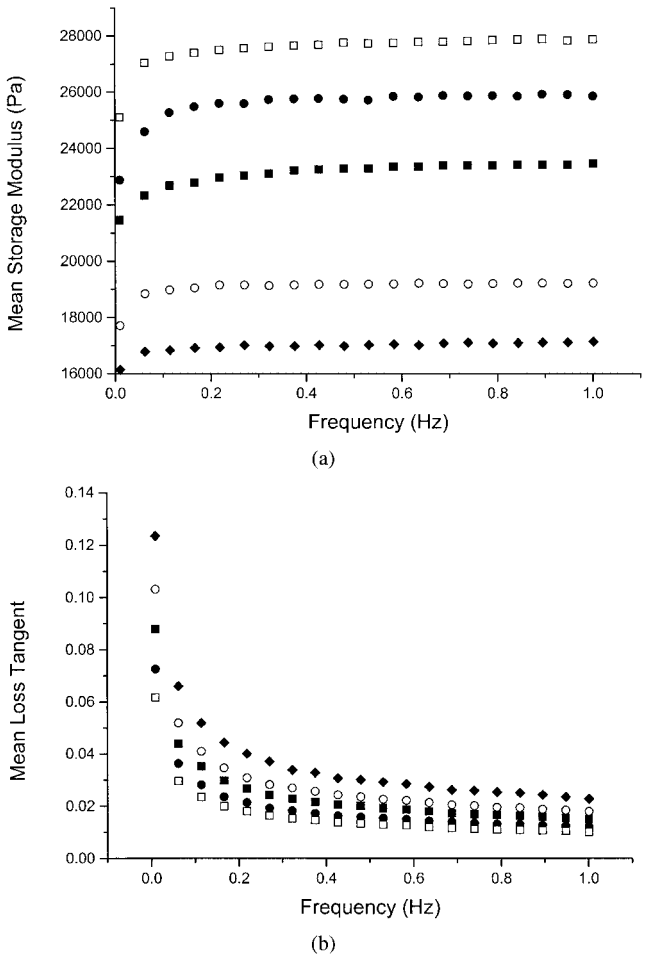


Figure 5 Effects of the oscillatory frequency on (a) G' and (b) tan δ for poloxamer 407 gels (25% w/w) containing different concentrations of glycerol: (■) 0, (●) 5, (□) 10, (○) 15, and (♦) 20%. Error bars have been omitted for clarity; however, the coefficient of variation was less than 8% in all cases.

the concentration of sodium chloride from 0 to 1 to 3% (w/w) significantly increased G' and reduced tan δ. G' of the poloxamer gel devoid of sodium chloride was statistically similar to that containing 5% (w/w) of this solute, although G'' and tan δ of the gel containing sodium chloride (5% w/w) were statistically lower. Similarly, gels containing 1 or 3% (w/w) sodium chloride exhibited statistically similar G' values, although the gel containing the higher concentration of this solute possessed significantly lower values of both tan δ and G''. Conversely, the addition of up to 3% (w/w) tetracaine hydrochloride to poloxamer 407 (25% w/w) did not significantly alter the viscoelastic properties of the poloxamer system. However, the addition of higher concentrations of this model therapeutic agent (5 and 7% w/w) significantly altered the viscoelastic character of the poloxamer system, notably significantly decreasing G' and increasing G'' and tan δ. These alterations were concentration-dependent.

DISCUSSION

The development of topical pharmaceutical products is regarded as a complex process, often involving the inclusion of several components to achieve the required clinical and nonclinical performance.[21,22] For example, the modification of the molecular weight of polymeric components may be employed to modify drug release and rheological properties, whereas the incorporation of cosolvents may be necessary to increase the solubility of the therapeutic agent or to improve the diffusion characteristics across the chosen substrate (e.g., skin).[21,22] Furthermore, such systems often require the inclusion of electrolytes (as buffers) and therapeutic agents, both of which may affect the mechanical properties of such systems. Because of their ability to undergo a sol–gel transition, poloxamers have been employed as topical drug delivery systems and, in certain clinical applications, have shown considerable promise.[10,11,12] However, although several studies have examined the flow properties of poloxamer systems, few have examined the structural rheology of such systems. This is an important omission as these properties are accepted to influence the clinical performance of topical systems.[14,17] Therefore, the selection of experimental parameters was designed to represent typical strategies that are available to the formulation scientist. Glycerol, propylene glycol, and ethanol are pharmaceutically acceptable solvent systems that are additionally known to enhance the diffusion of therapeutic agents across the skin,[21] whereas sodium chloride was chosen as a model monovalent electrolyte. Tetracaine hydrochloride was chosen as a model therapeutic agent, having been

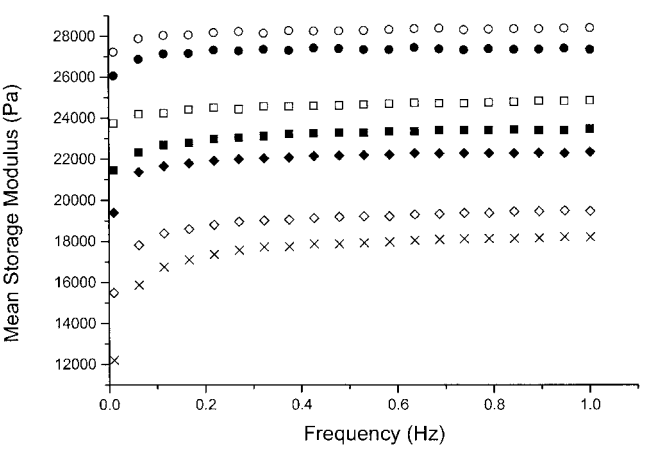


Figure 6 Effects of the oscillatory frequency on G' for poloxamer 407 gels (25% w/w) containing different concentrations of model solutes: (■) 0% (w/w) solute, (●) 1% (w/w) sodium chloride, (○) 3% (w/w) sodium chloride, (□) 5% (w/w) sodium chloride, (♦) 3% tetracaine hydrochloride, (◇) 5% tetracaine hydrochloride, and (×) 7% tetracaine hydrochloride. Error bars have been omitted for clarity; however, the coefficient of variation was less than 7% in all cases.

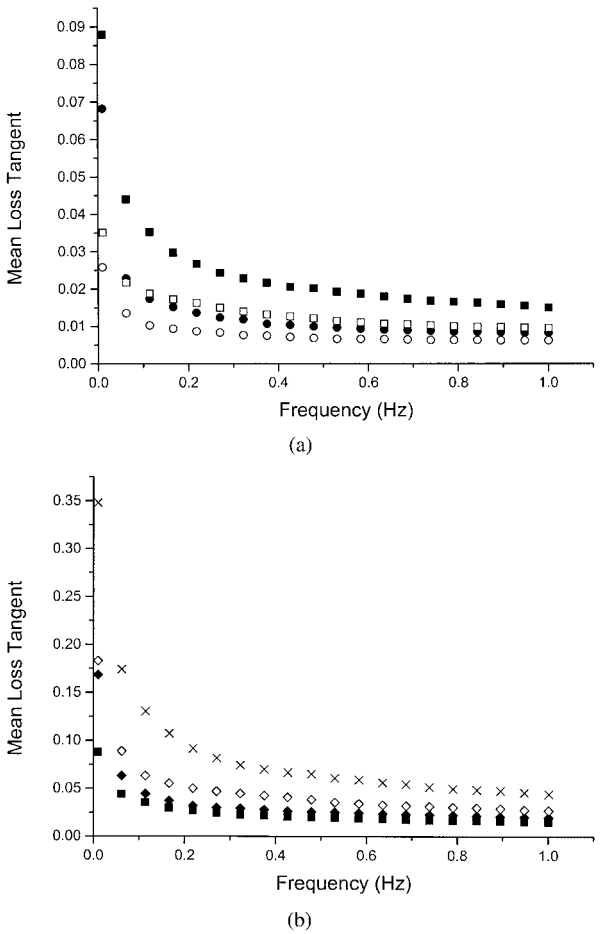


Figure 7 Effects of the oscillatory frequency on tan δ for poloxamer 407 gels (25% w/w) containing different concentrations of (a) sodium chloride or (b) tetracaine hydrochloride: (■) 0% (w/w) solute, (●) 1% (w/w) sodium chloride, (○) 3% (w/w) sodium chloride, (□) 5% (w/w) sodium chloride, (◆) 3% tetracaine hydrochloride, (◇) 5% tetracaine hydrochloride, and (×) 7% tetracaine hydrochloride. Error bars have been omitted for clarity; however, the coefficient of variation was less than 7% in all cases.

formulated as a topical gel formulation to provide percutaneous local anaesthesia,[21] whereas the choice of the poloxamer grade was intended to provide a wide range of molecular weights.

For the most part, the aqueous poloxamer solutions examined in this study exhibited thermal gelation characteristics that were dependant on the concentration and molecular weight of the poloxamer, the composition of the solvent, and the inclusion of solutes. At a low temperature in an aqueous solution, poloxamer molecules are surrounded by a sheath of hydrogen-bonded water molecules[1] and exist as monomolecular micelles in which the hydrophilic poly(oxyethylene) portions are coiled around the central hydrophobic poly(oxypropylene) portions.[2] In this state, there are few interactions between polymer molecules, and the chains are highly mobile. As a result, poloxamer solutions exhibit Newtonian flow characteristics.[3,4,23] Accordingly, in this study, the elastic properties of poloxamer sol systems were minimal and could be described as elastoviscous.

As the temperature is increased, the hydrogen bonds between the water sheath and the poloxamer chains [particularly the hydrophobic poly(oxypropylene) portions] become unstable, and eventually desolvation occurs, thereby facilitating extensive hydrogen bonding between poly(oxypropylene) moieties on neighboring chains.[3] The poly(oxypropylene) aggregates form the hydrophobic core of multimolecular micelles, with the hydrophilic poly(oxyethylene) portions interfacing with the aqueous vehicle. The formation of multimolecular micelles leads to a loss of chain mobility and the formation of a viscoelastic gel network, discernible by a sudden increase in G'. The formation of micellar gel networks has previously been reported to give rise to considerable viscoelastic properties in other pharmaceutical semisolids such as creams.[24,25] Above the critical micelle temperature (T_m), the poloxamer systems exhibited rheological properties that were typical of physically entangled (pseudocrosslinked) gels, evident from the relative plateau in G' over 2 decades of oscillation frequencies.[17,26] The poloxamer systems also exhibited low values for tan δ (<0.1), typical of gel behavior, indicating that viscous deformations contributed little to the overall strain and that the observed behavior was akin to an elastic solid. The gradual reduction in tan δ with increasing oscillation frequency indicated the modest time dependence of the viscous deformation. At a low frequency, there was sufficient time between oscillation cycles for considerable viscous deformation. However, at higher frequencies of oscillation, there was less time during each oscillation cycle for viscous deformation. Therefore, tan δ decreased. The resultant suppression of long-range molecular rearrangements in the poloxamer systems has been reported to be due to the formation of stable three-dimensional (cubic) micellar gel structures.[27] Interestingly, the magnitudes of tan δ for the poloxamer systems were comparatively small and were typical of solid polymer films. This is evidence of the high degree of polymer–polymer interactions in these systems, resulting in highly elastic behavior.

Poloxamer 188 has a molecular weight of 7680–9510, of which approximately 80% is poly(oxyethylene) and 20% is poly(oxypropylene).[28] For aqueous systems containing a constant total amount of poloxamer, T_m increased with increasing proportions of this lower molecular weight grade. With both grades present in the same system, gelation resulted from the formation of mixed micelles containing poloxamer molecules of both grades. The results of thermal oscillation studies suggest that the formation of the mixed micelles occurred in two stages. First, there was the formation of micelles consisting mainly of poloxamer

407 molecules. This accounted for the sudden increase in G' at T_m. In the second stage, lower molecular weight poloxamer 188 molecules were incorporated into these micelles, producing a continued increase in G'. As the proportion of poloxamer 188 increased, the concentration of poloxamer 407 subsequently decreased. Therefore, because of the greater separation, hydrophobic associations between poloxamer 407 molecules occurred less readily, T_m increased, and the elastic nature of the systems decreased (decreased G' and increased tan δ).

An increase in the total concentration of the poloxamer reduced T_m of each system. This can be attributed to the closer proximity of the polymer molecules in solution and a decrease in the amount of water available for the formation of the sheath that protected the hydrophobic regions from interactions at lower temperatures. As a result, intermolecular hydrophobic associations occurred more readily, and gelation occurred at a lower temperature. In fact, for the system containing 35% (w/w) poloxamer 407, there was insufficient water available to prevent gelation even at the lowest temperature. The increase in the total poloxamer concentration also increased the elastic properties of each gelled system, and this could be attributed to an increase in the volume of micelles in proportion to the volume of the surrounding water channels and the greater interaction between adjacent micelles. Interestingly, the statistical interaction between the poloxamer concentration and molecular weight blend provided an insight into the relationship between these two parameters. At the higher poloxamer concentration (35% w/w), the effects of the molecular weight blend on the viscoelastic properties were significantly less than at the lower concentration. Therefore, this would suggest that the closer proximity of the polymer molecules in solution (35% w/w) is sufficient to partially offset the deleterious effects of the shorter chain length poloxamer on polymer–polymer interactions. Furthermore, the rheological properties of poloxamer systems (25% w/w) may be more readily manipulated than those containing 35% (w/w) of this polymer.

For systems containing 25% (w/w) poloxamer 407, marked differences in the sol–gel transition and gel consistency were observed with the incorporation of organic cosolvents. T_m decreased with increasing proportions of ethanol, propylene glycol, or glycerol. This effect may be attributed to the dehydration of the poloxamer chains.[4] As the integrity of the water sheath was reduced, interactions between neighboring chains occurred more readily, and T_m was lowered. Interestingly, the effects of the three cosolvents on the rheological properties of the poloxamer systems were significantly different, as confirmed by the observed statistical interactions between the cosolvent type and concentration. In the presence of ethanol, the elastic nature of the resultant gels also generally decreased, as indicated by lower G' and higher tan δ values. This may be due to the effects of ethanol on the inhibition of hydrophobic interactions involved in micelle formation.[29] In the case of propylene glycol and glycerol, the incorporation of up to 15% propylene glycol did not generally affect the rheological properties of the gels. However, in the case of glycerol, the addition of up to 10% enhanced the elastic nature of the gels. It may be argued that these effects are due, at least in part, to alterations in the solubility parameter of the solvent, which, in turn, reduced the interaction of the polymer with the solvent. It might be expected that, at higher concentrations of the cosolvent, there would be a complete loss of rheological structure as the solubility parameter of the solvent deviates further from that of poloxamer. However, it is important to consider the effects of the alcohol structure on the rheological properties of the poloxamer systems. Ethanol, propylene glycol, and glycerol possess one, two, and three alcohol moieties, respectively. Because of their chemical nature, propylene glycol and glycerol may participate in hydrogen-bond formation with the ethereal oxygen atoms and the alcohol moiety of the poloxamers. Accordingly, propylene glycol and glycerol may act as crosslinking agents and, in so doing, may counter their effects on the solubility parameter of the solvent. In this scenario, the degree of crosslinking that may be offered by glycerol will be greater than that of propylene glycol, as the former can participate in network formation. The disparities in the effects of these solvents on the rheological properties of poloxamers may, therefore, be partially due to this ability. As ethanol possesses only one alcohol function, it will not participate in crosslinking interactions; accordingly, no rheological structuring is observed.

Marked differences in the sol–gel transition and rheological properties of systems containing 25% (w/w) poloxamer 407 were also observed with the incorporation of organic and inorganic solutes. Distinct, concentration-dependent decreases in T_m were observed with the incorporation of sodium chloride. This effect can be viewed as a reduction in the water activity (as some of the water is required for the solvation of ions) and an increase in the effective concentration of the polymer.[29] At low concentrations of sodium chloride, there was an increase in the elastic nature of the gelled system, indicated by increases in G' and decreases in tan δ. This is consistent with the observation of the increased viscosity of poloxamer solutions in the presence of strong electrolytes.[4,5] In the presence of strong electrolytes, the energy required to attain a given level of desolvation is reduced. Therefore, gels containing sodium chloride had a higher aggregation number than a gel without this salt at the same temperature. At higher concentrations of sodium chloride, there was a reduction in

the poloxamer gel structure, indicated by a reduction in G' and an increase in tan δ. This finding is consistent with the earlier report by Schmolka,[1] who suggested that strong electrolytes disrupted the poloxamer micelle structure. However, it is important to note that the viscoelastic properties of poloxamer gels containing 5% sodium chloride were statistically similar to those of comparison systems that were devoid of this electrolyte.

Conversely, the incorporation of tetracaine hydrochloride (a monovalent organic ion) into the aqueous poloxamer gel increased T_m and reduced the gel strength (decreased elastic modulus and increased tan δ). These effects are inconsistent with the effects of monovalent electrolytes, as shown previously,[1] and so other factors must contribute to these observations. First, tetracaine possesses amphiphilic activity[30] and may, therefore, affect the micelle formation of poloxamers. As micelle formation is the prelude to poloxamer gelation, these observations concerning their effects on the sol–gel temperature and the viscoelastic properties of the resultant gel would suggest that the effects of tetracaine hydrochloride are due to interference with the formation and/or architecture of poloxamer micelles. This is consistent with a previous report in which the decreased gel strength associated with the presence of surfactant molecules was suggested to be due to effects on poloxamer micelle formation.[1] This observation is of particular importance to the pharmaceutical formulator for two reasons. First, many therapeutic agents that are formulated for topical administration are water-soluble and will, therefore, dissolve in aqueous poloxamer systems. Second, many therapeutic agents possess surfactant activity.[30] Therefore, care must be shown in the formulation of poloxamer systems with dissolved therapeutic agents, or a modification of the rheological structure may result.

CONCLUSIONS

This study has examined the effects of polymer molecular weight blends, solutes, and cosolvents, chosen according to their availability to, and history of usage by, pharmaceutical formulators, on the thermorheological properties of aqueous poloxamer systems. In particular, the study has shown that alterations in the molecular weight poloxamer blend significantly altered T_m and the elastic nature of the gelled system. Furthermore, the incorporation of alcoholic cosolvents altered these properties, with ethanol, propylene glycol, and glycerol reducing the sol–gel temperature in a concentration-dependent fashion. The elastic nature of the gelled poloxamer systems was compromised by the inclusion of these alcohols, although the greatest tolerance to rheological modification was shown by glycerol, and the lowest tolerance was shown by ethanol. Interestingly, at lower concentrations, the elastic nature of the poloxamer systems was enhanced by the presence of propylene glycol and glycerol. The inclusion of a model monovalent inorganic solute, sodium chloride, initially reduced the sol–gel temperature and increased the elastic nature of the gel. However, this effect was reversed at higher concentrations (5% w/w). Interestingly, the inclusion of a model therapeutic agent employed for percutaneous local anesthesia, tetracaine hydrochloride, increased T_m and reduced the elastic properties of aqueous poloxamer systems in a concentration-dependent fashion.

Aqueous poloxamer solutions provide an attractive option for the pharmaceutical scientist for the formulation of topical drug delivery systems, as they exhibit a predominantly elastic response to oscillatory stresses and G' which is almost entirely independent of the oscillatory frequency. However, this study has shown that the incorporation of common components of topical drug delivery systems, including therapeutic agents, may dramatically affect the thermorheological properties of poloxamer systems. A reduction in T_m may render the formulations unsuitable for applications, whereas increasing the sol–gel temperature may prevent gel formation at physiological temperatures, thereby negating the benefits of these systems as topical dosage forms. Alterations in the viscoelastic properties of aqueous poloxamer systems will have implications for their clinical performance, as it has been reported that structural rheological properties (elasticity) directly influence drug delivery and retention at the site of application.[17,31,32] Therefore, this study has highlighted the need for the rational selection of components in the formulation of poloxamer systems as platforms for topical drug delivery.

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