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Rheological properties of poloxamer vehicles

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Summary

The rheological behavior of poloxamer vehicles as a function of composition and temperature was evaluated using continuous shear methods. For poloxamer vehicles in the sol state (low concentration and temperature) a linear relationship was observed between shear rate and shear stress. For some of the vehicles, as concentration or temperature was increased, the systems underwent a sol–gel transition and their rheological behavior became non-Newtonian.The addition of sodium chloride or polyhydroxy compounds such as glycerin or propylene glycol to the vehicles produced an increase in their apparent viscosities. At low temperature (5°C) apparent viscosities were exponentially related to concentration. As temperature was increased to 15°C, positive deviations from the expected viscosities were observed at the higher polymer concentrations.

Introduction

Poloxamers are poly(oxyethylene)poly(oxypropylene) block copolymers with the following chemical structure:

$$HO(CH_2CH_2O)_a(CH[CH_3]CH_2O)_b(CH_2CH_2O)_cH$$

where a and c are statistically equivalent (BASF Wyandotte, OS-796). A series of

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poloxamers, which vary over a wide range of molecular weight and relative proportion of oxyethylene and oxypropylene moieties, are commercially available [1].

Some poloxamers possess properties which appear to make them particularly suitable for use in the formulation of topical dosage forms; these include their relatively low toxicity and ability to form clear gels in aqueous media (BASF Wyandotte, OS-3012(765)). In recent years, a number of poloxamer-containing formulations have been evaluated as novel dosage forms, either for dermatological use (Schmolka, 1972; Chen-Chow and Frank, 1981) or topical ophthalmic application (Waring and Harris, 1979; Miller and Donovan, 1982). For application to the skin, such water-based polymeric gels offer several advantages over traditional oleaginous bases in terms of ease of application, cosmetic acceptance (colorless and water-washable) and good drug release characteristics. Similarly, for topical ophthalmic use, semi-solid gels are better retained in the precorneal area than aqueous solutions but do not seem to cause as many visual disturbances as ointments do.

Poloxamers are more soluble in cold water than in hot, which has been attributed to extensive hydrogen bonding between water molecules and the ethereal oxygen atoms of the polymer (BASF Wyandotte, OS-796). Similar solubility dependence on temperature has been observed for methylcellulose and high molecular-weight polyethylene glycol (Schott, 1980). The decrease in solubility with an increase in temperature is due to less extensive hydration at higher temperatures caused by breakage of hydrogen bonds.

In aqueous solution poloxamers are surrounded by a hydration layer or sheath of water molecules. Extensive polymer–solvent interactions cause the poloxamer to become extended; entanglement of the long, thread-like molecules leads to an increase in solution viscosity. At sufficiently high polymer concentration, some poloxamer–water mixtures will gel. Such gels have been reported to exhibit reverse thermal gelation behavior; their macroscopic viscosity increases with an increase in temperature (Schmolka, 1972; Chen-Chow and Frank, 1981). Similar behavior has been reported for methylcellulose and high molecular-weight polyethylene glycol solutions which gel upon heating and melt on cooling (Schott, 1980). At higher temperatures, poloxamer desolvation and enhanced polymer entanglement may contribute to gel formation. *Intermolecular* hydrogen bonding, that is, hydrogen bonding between ethereal oxygen atoms and the hydrogen atoms of either of the terminal, primary hydroxyl groups may also promote gelling. The number of interactions with neighboring chains will increase as the concentration of polymer increases.

The studies described below were undertaken to characterize the rheological behavior of a number of different poloxamer systems, as a function of composition and temperature. The results will aid in identifying vehicles which would be suitable for use in the development of dosage forms for dermatological and ophthalmic drug delivery.

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[1] Pluronic^{R}, BASF Wyandotte Corp., Wyandotte, MI.

Materials and Methods

Materials

Poloxamers were a gift from BASF Wyandotte, Wyandotte, MI. All other chemicals were of reagent grade and distilled water was used in all formulations.

Methods

All poloxamer formulations were prepared on a weight percentage basis using the cold method of preparation (BASF Wyandotte, OS-796). Formulations containing one or more of 4 different poloxamers were studied. These included the following poloxamers: (1) 238 (Pluronic F-88); (2) 335 (Pluronic P-105); (3) 403 (Pluronic P-123); and (4) 407 (Pluronic F-127). These poloxamers were selected to obtain a group which varied relative to their molecular weight and relative degree of hydrophilicity. Some of the physical characteristics of these polymers are summarized in Table 1.

The rheological properties of the poloxamer systems were assessed by continuous shear methods using a Wells-Brookfield microviscometer. This cone-plate viscometer has a jacketed sample cup which allows the temperature to be thermostatically controlled. Studies were conducted using a cone having a radius of 2.4 cm and angle of 0.8°. The sample volume was 450 μl and was subjected to shear rates ranging between 3.75 and 750 s^{-1}. The full scale torque of the instrument was 57,496 dyne · cm. Samples were cycled through 8 speeds (up-down) over a total cycle time of 3.75 min.

The rheology studies were conducted at 5, 15, 25 and 35°C in order to characterize the viscosity of the vehicles over a wide range of temperatures. The results from the studies conducted at the two higher temperatures will be reported in a later communication.

The reproducibility of the data was assessed by determining the rheograms at 5 and 15°C for the 25% poloxamer vehicles, with and without organic additives, in triplicate. Viscosities obtained from the individual runs were averaged and the coefficients of variation were calculated. In general, the coefficient of variation increased with a decrease in the average viscosity. The coefficients of variation for

TABLE 1

PHYSICOCHEMICAL CHARACTERISTICS OF SELECTED POLOXAMERS (BASF WYANDOTTE, OS-796)

Poloxamer	238	335	403	407
Trade name	F-88	P-105	P-123	F-127
Molecular weight	10800	6500	5750	12500
POE : POP ratio	80.20	50:50	30:70	70:30
Hydrophobe weight (POP)	2160	3250	4025	3750
HLB at 25°C	28	15	8	22
Gel range	40–90%	30–90%	30–90%	20–90%

TABLE 2

VISCOSITY OF POLOXAMER VEHICLES (cps) AS A FUNCTION OF CONCENTRATION AT 5 AND 15°C

	238	335	403	407
5°C				
15%	22	13	11	19
20%	42	22	19	38
25%	75	38	36	67
30%	136	65	52	120
35%	231	116	88	340
15°C				
15%	15	9	7	14
20%	28	14	11	24
25%	49	28	23	59
30%	90	108	93	gel
35%	215	gel	gel	gel

the 13 vehicles evaluated in this manner ranged from 2.2 to 9.8% Thus, the data obtained was considered to be reasonably reproducible.

Results and Discussion

Viscosity as a function of poloxamer concentration

A series of 20 poloxamer gels, containing either poloxamer 238, 335, 403 or 407 were prepared in water at concentrations of 15, 20, 25, 30 and 35%. At 5°C, all of the systems displayed Newtonian behavior with a linear relationship existing between shear rate and shear stress. The viscosities (cps) determined from the rheograms are summarized in Table 2. Although the concentration dependency of viscosity is somewhat gradual in the range of 15–30%, there was a marked increase in the viscosities of the systems above 30%. At 5°C, the difference in viscosity between poloxamers was minimum at low concentration and gradually increased.

The data given in Table 2 were examined to determine whether they adhered to the following equation:

$$\eta = \eta_0 e^{kc} \tag{1}$$

which describes apparent viscosity as a function of concentration (Chase, 1970). At 5°C, the logarithm of the viscosity appeared to correlate reasonably well with the concentration of poloxamer. The following values were obtained for the slope, intercept and correlation coefficient for each of the poloxamers:

Poloxamer	Slope	Intercept	Corr.
238	0.118	1.36	0.9995
335	0.109	0.914	0.9999
403	0.103	0.888	0.9969
407	0.138	0.821	0.9926

Schmolka (1977) reported that the thickening power of poloxamers in water increases as the hydrophobe molecule weight increases and as the ethylene oxide/propylene oxide ratio increases. The data in Table 2 suggests that, for a given poloxamer concentration, an increase in degree of poloxamer hydrophilicity caused an increase in apparent viscosity. However, at equal concentrations (on a weight percentage basis), the apparent viscosities of the poloxamers studied did not increase with an increase in the molecular weight of the hydrophobe (Table 1). When Eqn. 1 is used to describe the relationship between apparent viscosity and concentration, our data generally suggested that the concentration dependency of viscosity (as indicated by the magnitude of the slope, k) was greater for higher molecular weight polymers than those with relatively low molecular weight. Our data indicates that the generalities made relative to viscosity and hydrophobe molecular weight (Schmolka, 1977; BASF, OS-796) may be misleading.

As the temperature was increased to 15°C, similar trends were noted. From the data listed in Table 2, it can be seen that at relatively low concentration (i.e. 25% or less), the poloxamer systems exhibited normal behavior in that the viscosity of the vehicles decreased with an increase in temperature. In fact, for poloxamer 238, this trend held throughout the range of concentrations investigated. On the other hand, formulations containing either poloxamer 335, 403 or 407 at concentrations greater than 25% exhibited reverse-thermal behavior, in that the macroscopic viscosity of the vehicles increased with an increase in temperature.

The data obtained at 15°C were also examined for adherence to Eqn. 1. At this temperature, however, only the poloxamer 238 data followed the expected relationship ($S = 0.130$, $i = 0.714$, corr. = 0.9962). For the remaining poloxamers, a non-linear relationship was observed between the logarithm of viscosity and concentration; at high polymer concentrations, positive deviations from the expected viscosities were observed.

As noted in Table 2, some of the formulations, containing higher percentages of poloxamer, gelled at 15°C. In general, the gelled systems appeared to undergo shear-thinning although they did not clearly display either pseudo-plastic or simple plastic flow. At present, alternative methods are being used to characterize the rheological behavior of such gelled systems.

Mixed poloxamer systems

The rheological behavior of the 6 possible binary mixtures of these 4 poloxamers was also investigated at 5 and 15°C. In all cases, the formulations were 75% water, the concentration of each poloxamer being 12.5%. The results of the experimentally determined viscosities are summarized in Table 3. Assuming that interactions between two different poloxamers in solution are similar in nature and magnitude to interactions between like poloxamers, a theoretical viscosity was calculated for each binary mixture, based on the viscosities obtained for the individual poloxamers at 25%.

Comparison of the data in Table 3 indicates that there was reasonable agreement between the experimentally determined and theoretically calculated viscosities for the binary mixtures. In most cases, the measured value was slightly less than the

TABLE 3

APPARENT AND THEORETICAL VISCOSITIES (cps) OF BINARY POLOXAMER MIXTURES

Binary mixture	5°C		15°C	
	Apparent viscosity	Theoretical viscosity	Apparent viscosity	Theoretical viscosity
238–335	48	57	34	39
238–403	48	55	31	36
238–407	69	71	49	55
335–403	34	37	23	26
335–407	53	53	46	44
403–407	47	51	39	41

theoretical value; the statistical significances of these differences were not determined.

Organic additives

The effect of organic modifiers on the viscosity of poloxamer 407 systems at various temperatures were also evaluated. The specific compounds selected were glycerin and propylene glycol. It was felt that such compounds might be required in topical gel formulations, to act as humectants, to prevent drying and crusting of the vehicles.

At low temperature (5°C) and low concentration of organic modifier (1%), there was little difference in viscosity, relative to the control vehicle (25% poloxamer 407), as noted in Table 4. As the concentration of organic additive increased, however, the viscosity of the systems increased. While propylene glycol appeared to be somewhat more effective than glycerin at increasing viscosity, the differences in viscosity at 5 and 10% additive were not statistically significant.

TABLE 4

EFFECT OF GLYCERIN, PROPYLENE GLYCOL AND SODIUM CHLORIDE ON THE VISCOSITY (cps) OF 25% POLOXAMER 407

Vehicle	5°C	15°C
Control	67	59
1% glycerin	68	69
5% glycerin	81	180
10% glycerin	110	gel
1% propylene glycol	68	65
5% propylene glycol	82	150
10% propylene glycol	120	500
1% sodium chloride	69	180
5% sodium chloride	700	gel

At 15°C, the presence of both compounds again increased vehicle consistency, but the trend was reversed; the presence of glycerin caused a greater increase in viscosity than propylene glycol. Viscosity differences were significant at 5 and 10% additive. In fact, the 10% glycerin system gelled at 15°C, whereas the propylene glycol system remained fluid. At 25°C, all of the formulations studied gelled and the difference in the rheological behavior of the systems tended to be less marked.

In general, the addition of alcohol to aqueous solutions of hydrophilic and water-soluble polymers may cause precipitation or gelation because: (1) alcohol is a non-solvent or precipitant, lowering the dielectric constant of the medium; and (2) alcohol tends to dehydrate the hydrophilic solute (Schott, 1980a). Polyhydroxy compounds such as glycerin and propylene glycol have been reported to increase the viscosity of solutions of other hydrophilic polymers such as sodium alginate and sodium carboxymethylhydroxyethyl cellulose (Martin et al., 1964). Such increases in viscosity have been attributed to an enhanced polymer interaction in solution or a specific association between the polymer and the polyhydroxy compound.

Barry and Meyer (1979) have studied the rheological behavior of 3% gels of Carbopols 940 or 941 in neat glycerin, propylene glycol and ethylene glycol. For unneutralized systems, the apparent viscosities decreased with decrease in solvent molecule size. This behavior paralleled the viscosity order of the pure solvents. For neutralized gels, however, the ethylene glycol systems remained lower in consistency than the glycerin systems but were higher in consistency than the propylene glycol systems. They concluded that the change in behavior was probably caused by changes in solvation and/or molecular shape and that consistencies depend more on the nature of the solvent than on its molecular size and inherent viscosity (Bary and Meyer, 1979).

Poloxamer 407 has been reported to have a solubility of less than 1 g/100 ml in glycerin and propylene glycol, whereas its solubility in water is greater than 10 g/100 ml (BASF, OS-796). Thus, in the hydroalcoholic vehicles studied, poloxamer 407 would be less extensively solvated than in water. Desolvation, enhanced polymer entanglement and more extensive intermolecular hydrogen bonding may all lead to a more structured vehicle, hence, increasing vehicle viscosity.

Electrolytes

The effect that the presence of a strong electrolyte would have on the viscosity of poloxamer gels was determined using a 25% poloxamer 407 vehicle containing sodium chloride. The results obtained with systems containing either 1% or 5% sodium chloride, in 25% poloxamer 407, at 5 and 15°C are also summarized in Table 4.

Like the organic additives, the presence of sodium chloride in the formulations increased the viscosity of the poloxamer systems. The effect, however, appeared more pronounced on a percentage basis.

The effectiveness of electrolytes to salt out, precipitate or gel hydrophobic colloidal systems depends on the extent of hydration of the electrolytes. In general, salts raise the temperature of precipitation or gelation of most hydrophilic colloidal solutions or their gel melting points. Exceptions among hydrophilic colloids are methylcellulose, hydroxypropyl cellulose and polyethylene oxide whose gelation temperatures or gel points and gel melting points are lowered by salting out (Schott, 1980a).

From the data it can be noted that the presence of 5% sodium chloride in 25% poloxamer 407 decreased the sol–gel transition point sufficiently for the vehicle to become semi-solid at 15°C. Thus, poloxamer 407 behaves more similarly to methylcellulose than other hydrophilic colloids relative to its tendency to salt-out of aqueous solution in the presence of a strong electrolyte such as sodium chloride.

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