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Aggregation and gelation of a polymerisable diacryloyl derivative of poloxamer 407

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Summary

The diacryloyl derivative of poloxamer 407 has been prepared and its aggregation and gelation properties in solution studied. With increasing temperature over the range 25–50 °C the hydrodynamic diameter of aggregates decreased from 274 to 69 nm, in contrast to unmodified poloxamer 407 where the hydrodynamic size remains constant. Hydrogels can be formed by polymerisation of the diacryloyl derivative in aqueous solution: such hydrogels can absorb water up to 1600% of their initial dry gel weight. Ethanol inhibits gelation and this has been shown to be due to the fact that only small, possibly monomolecular, micelles are formed in such mixed solvent systems.

Introduction

Poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) (PEO-PPO-PEO) block co-polymeric surfactants (poloxamers or Pluronics™) have low toxicities and are widely used in pharmaceutical systems as solubilising, emulsifying and wetting agents. They are available in a wide range of HLBs through variation of the PEO and PPO block sizes. In recent years, new applications of poloxamers have been developed in drug delivery systems, e.g. when used to form hydrogels (Al-Saden et al., 1980; Law et al., 1984, 1986a), to stabilise multiple emulsions by interfacial polymerisation of a poloxamer derivative (Law et al., 1986b) or by interfacial complexation (Law et al., 1986c).

Following modification of poloxamers to form diacryloyl derivatives (Law et al., 1984), polymerisation may be initiated (in bulk or solution) by chemical methods or through ultraviolet or γ-irradiation. The diacryloyl derivative of poloxamer 407, a hydrophilic poloxamer (with an HLB value of 22) with an ethylene oxide content of 70% and molecular weight of 12 500, has been investigated in detail in this paper to follow its aggregation and gelation behaviour in solution: solution properties of the unmodified molecule have been studied previously (e.g. Rassing and Attwood, 1983; Attwood et al., 1984, 1985). Of particular interest is the fact that aqueous poloxamer 407 solutions, fluid at room temperature, gel at body

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temperature (Chen-Chow and Frank, 1981; Attwood, 1985).

As the properties of the hydrogel depends to some extent on the solution properties of the monomer, we initiated a study, described here, of the crosslinking of a poloxamer 407 derivative at a range of temperatures when it was anticipated that the monomer would exist in different states of aggregation.

Viscometric techniques and photon correlation spectroscopy have both been used in this paper to study the aggregation and gelation of the diacryloyl derivative of poloxamer 407. Previously, we have prepared and studied hydrogels from the diacryloyl derivatives of poloxamers 181 and 188 and various mixtures of the two derivatives (Law et al., 1984, 1986a).

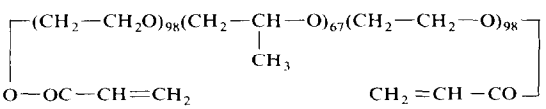
Materials and Methods

Materials

Poloxamer 407 was obtained from BASF. Acryloyl chloride was from Aldrich, U.K. and potassium persulphate from BDH, U.K. Water was double distilled.

Derivatization of poloxamer 407

The diacryloyl derivative of poloxamer 407 was prepared in dry toluene at 40 °C according to the method of Law et al. (1984), using a 5 : 1 molar ratio of acryloyl chloride to poloxamer 407 with triethylamine as catalyst. After purification by column chromatography and re-precipitation the material was characterised by infrared spectroscopy. The structure is as follows:



The abbreviation VP407 will be used for this derivative of the parent compound.

Cross-linking of VP407

Cross-linking of the diacryloyl poloxamer was initiated by 0.1% potassium persulphate added to solutions of VP407 at various temperatures for periods of up to 3 h. Resulting hydrogels after washing in water were dried in vacuo at room temperature.

Swelling

A gel swelling index (GSI) was defined as

$$\mathrm{GSI} = (W_t/W_0 - 1) \times 100\%$$

where W_t after time t is the weight of sample (with external fluid removed with a tissue) after swelling and W_0 is the initial weight of hydrogel.

Viscometry

Viscometric measurements were made using an Ostwald viscometer with a flow time of 262 s for water at 25 ± 0.01 °C. Intrinsic viscosities were obtained from extrapolation of specific viscosity vs concentration plots to $c = 0$, and the Huggin's constant, K_H, calculated using the equation

$$\eta_{sp}/c = [\eta] + [\eta]^2 K_H c$$

Photon correlation spectroscopy (PCS)

PCS measurements were made with a Malvern K7027 LogLin correlator with 60 linear channels with a Liconix He/Cd laser (approx. 10 mW) at 441.6 nm. The time delay of the autocorrelation function was analysed by the method of cumulants (Koppel, 1972) to give the diffusion coefficient, hydrodynamic radius via the Stokes-Einstein equation and a polydispersity index. Solutions were filtered through 0.45 μm Millipore filters into glass cells maintained at a constant temperature (normally 25 °C) and measurements were made at a scattering angle of 90° unless otherwise indicated.

Results and Discussion

Aggregation behaviour in solution

The concentration dependence of the hydrodynamic diameter and the diffusion coefficient of the diacryloyl derivative of poloxamer 407, VP407, at 25 °C is shown in Table 1 and Fig. 1, respectively. Measurements were not possible below a

TABLE 1

PCS data for VP407 at various concentrations (25 °C)

Concentration (% w/v)	D_h (nm)	$D(\times 10^{-8})$ ($cm^2\ s^{-1}$)	Polydispersity index
0.25	132.7	3.67	0.33
0.375	141.4	3.41	0.29
0.50	147.6	3.28	0.29
0.75	161.8	3.00	0.27
1.00	177.9	2.75	0.27
2.00	229.3	2.14	0.35
3.00	249.2	1.96	0.52
4.00	273.8	1.82	0.67

concentration of 0.25% due to the low level of scattering. The increase in apparent size with concentration may be due to an increase in aggregation number. A sample of the unmodified poloxamer 407 at 25 °C has been reported to have an aggregation number of 6.9 and to be hydrated to the extent of 7.0 g H_2O per g 407 (Attwood et al., 1985). Over the concentration range 2–5% the hydrodynamic diameter was essentially constant at 20 nm (Attwood et al., 1984) although a size increase was found at concentrations of 10–15%. The replacement of the terminal hydroxyl groups of poloxamer 407 by the more hydrophobic acryloyl groups would be expected to increase the aggregation number. A similar modification to Triton X-100 reduced its cloud point by 53 °C (Whateley et al., 1977).

The relatively high polydispersity (0.3–0.7) may

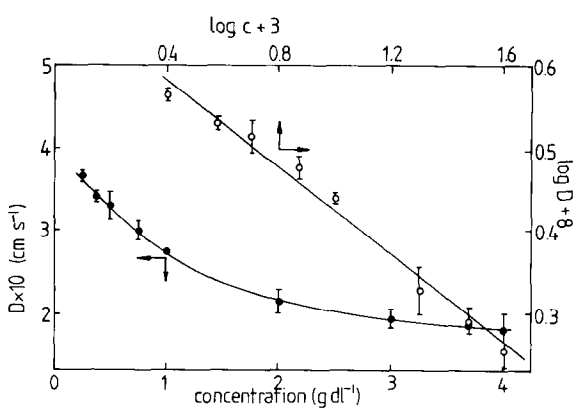


Fig. 1. Concentration dependence of diffusion coefficient of VP407 at 25 °C.

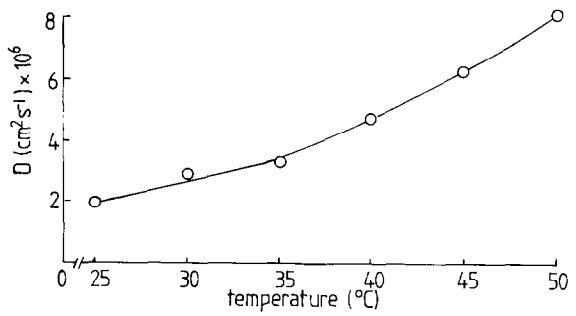


Fig. 2. Temperature dependence of diffusion coefficient of 4% VP407.

reflect the polydispersity in chain length in the commercial products, a factor which can vary from batch to batch (Attwood et al., 1985).

The variation of diffusion coefficient in 4% VP407 with temperature is shown in Fig. 2. The increase in diffusion coefficient (equivalent to a decrease in hydrodynamic diameter from 274 to 69 nm) over the temperature range 25–50 °C is very different from the behaviour of the unmodified poloxamer 407 where the hydrated diameter remains unchanged at approx. 20 nm with temperature.

Attwood et al. (1984, 1985) have shown that this constancy of hydrodynamic size as determined by PCS is a consequence of a concomitant increase in aggregation number and decrease in hydration. These two effects result in the gelation of such systems above a certain temperature and above a minimum concentration. In the modified material the two effects do not balance as temperature is raised, the greater hydrophobicity of the acryloyl derivative probably reducing the scope for dehydration as temperature is raised. The major aim of this work was to investigate the formation of hydrogels by cross-linking of the diacryloyl derivative.

In 30% (v/v) ethanol, no aggregates could be detected by PCS at concentrations up to 80%. In general, the length and solubility of the more soluble section of the co-polymer has a larger influence on micellar size (Bahadur et al., 1985); ethanol, which is a poorer solvent than water for the hydrophilic oxyethylene chains, probably induces VP407 to form monomolecular 'micelles' (not detectable by our light scattering instrumen-

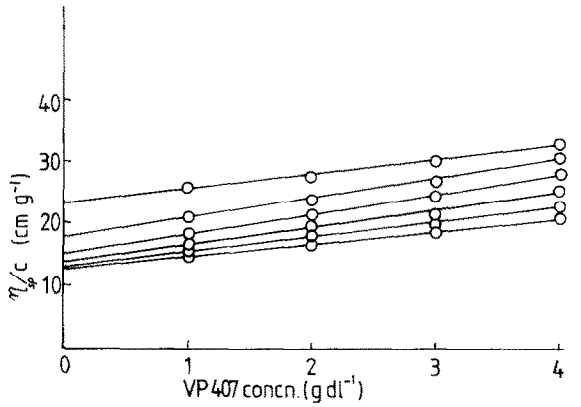


Fig. 3. Viscosity of VP407 in water at various temperatures (top curve, 25 °C; bottom curve, 50 °C in 5 °C intervals).

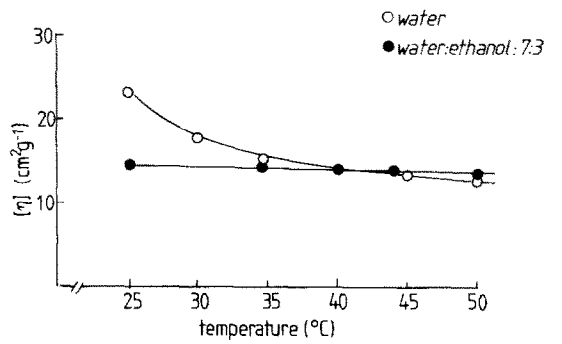


Fig. 4. Intrinsic viscosity of VP407 in water and water-ethanol (1 : 3) at various temperatures.

tation) rather than the multimolecular aggregates which form in water.

The intrinsic viscosities of VP407 in water at various temperatures are derived from the linear plots of reduced viscosity vs concentration shown in Fig. 3. The intrinsic viscosity at 25 °C in water (23.1 $cm^3\ g^{-1}$) is significantly higher than the value in 30% ethanol (14.8 $cm^3\ g^{-1}$), in agreement with the PCS data. In the mixed-solvent system there is little decrease with temperature (up to 50 °C) whilst in aqueous solution the intrinsic viscosity decreased from 23.1 to 12.3 $cm^3\ g^{-1}$ at 50 °C whilst the Huggin's constant increases (see Table 2 and Fig. 4).

The unmodified poloxamer 407 shows a decrease in hydration with increase in temperature as indicated by viscometric measurements (Attwood et al., 1985). The decrease in intrinsic viscosity of the modified poloxamer VP407 also indicates a decrease in hydration but without total intensity light scattering data it is not possible to interpret completely the hydrodynamic size data (which show a decrease in size with temperature) together with those from viscometry.

Polymerisation and gelation

Table 3 shows the minimum concentrations of VP407 necessary for gelation to occur in 3 h in the presence of 0.1% $K_2S_2O_8$ in water, 30 and 70% ethanol at temperatures between 45 and 80 °C. The presence of ethanol inhibits gel formation: e.g. at 50 °C the concentrations required are 3, 6 and 14% in water, 30 and 70% ethanol, respectively. As both the PCS and viscometric studies of VP407 in mixed ethanol-water solvent have shown the presence of small, possibly mono-molecular micelles, such entities are less likely to be able to form inter-molecular cross-links, as required for gel formation. The much larger multimolecular

TABLE 2

Effect of temperature on the intrinsic viscosity of VP407 in water and in 30% (v/v) ethanol

Temperature (°C)	Water		30% (v/v) ethanol solution	
	$[\eta]$	K_H	$[\eta]$	K_H
25	23.08	0.454	14.57	2.24
30	17.50	1.079	14.87	2.36
35	15.19	1.403	14.10	2.41
40	13.94	1.408	13.77	2.54
45	13.14	1.418	13.71	2.63
50	12.32	1.428	12.95	3.04

TABLE 3

Minimum concentrations (in %) for gelation in various solvent systems at various temperatures

Temperature (°C)	Water	30% (v/v) ethanol solution	70% (v/v) ethanol solution
45	4	12	–
50	3	6	14
55	–	4	10
60	2	–	–
80	1	–	–

0.1% (w/w) $K_2S_2O_8$ was used as catalyst.

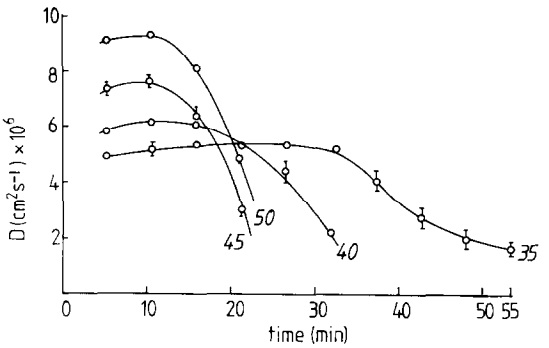


Fig. 5. Time dependence of diffusion coefficient of initiated aqueous VP407 solutions at 35–50 °C.

and, probably more unfolded aggregates, in aqueous solution will permit cross-linking and gel formation at lower concentrations.

The onset of gelation can be correlated with a rapid decrease in the diffusion coefficient of the micellar species as determined by PCS. These results at temperatures of 35–50 °C are shown in Fig. 5 for 8% VP407 solutions in water with 0.1% potassium persulphate as polymerisation initiator. As expected, the time of onset of gelation decreases with temperature, with times of approx. 15 min being adequate at 45 and 50 °C. It is interesting to note the small initial increase in diffusion coefficient (decrease in micellar size) prior to gelation: cross-links will be formed during this period, possibly within micellar aggregates leading to a slightly more compact packing.

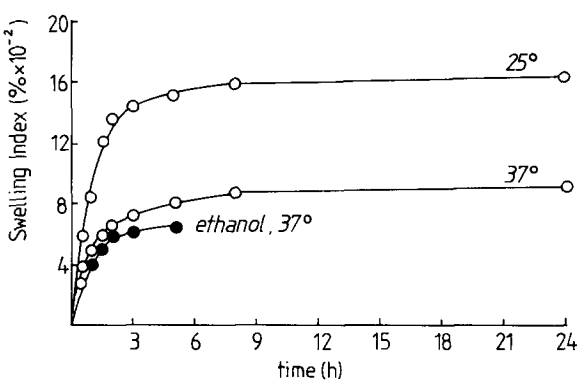


Fig. 6. Swelling of hydrogels prepared from 10% VP407 in 30% ethanol.

Gelation at 45 and 50% was followed over a longer period of time (up to 6 h) and at a lower concentration (2%) by determining the reduced viscosity after fixed times at the relevant temperature in the presence of potassium persulphate (0.1%). A small initial decrease in reduced viscosity is followed by a greater increase over several hours.

Hydrogels formed from concentrations of VP407 of less than 10% did not retain their integrity when dried in vacuo at room temperature. The swelling of hydrogels from 10% VP407 in 30% ethanol is shown in Fig. 6. This hydrogel absorbs water at 25 °C up to 1600% of its initial weight; at 37 °C hydration of the PEO chains is less and water uptake is reduced to 920%. Ethanol has less affinity for the hydrophilic PEO chains and uptake is 680% at 37 °C.

The diacryloyl derivative of poloxamer 407 shows temperature-dependent aggregation behaviour which is different from that of the unmodified poloxamer 407. The balance between micellar aggregation and dehydration in poloxamer 407 is disturbed by replacement of the terminal hydroxyls with acryloyl groups. However, the modified form can be cross-linked in aqueous solution to form reversible swellable hydrogels, the properties of which are dependent on the temperature of production.

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