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The effect of gamma irradiation on the surface, rheological and micellar behaviour of the block copolymer, Tetronic 908

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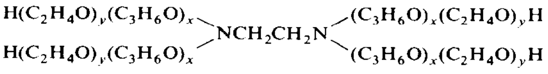
Summary

The poly(oxyethylene)-poly(oxypropylene) block copolymer, Synperonic (Tetronic) T908, is a poloxamine which forms micelles in aqueous solution over the temperature range 30–50 °C. Photon correlation spectroscopy studies have shown increases of mean micelle size and polydispersity of this poloxamine with increase of solute concentration in aqueous solution, leading eventually to the reversible gelation of the solutions at concentrations above approx. 20% w/w. Exposure of solutions of T908 to doses of gamma radiation up to 1.2 Mrad induced gelation at lower poloxamine concentrations than in nonirradiated systems. Irradiation had no detectable effect on the aggregation number of the micelles or the critical micelle concentration but caused a significant increase of micellar hydration. Temperature increase between 30 and 50 °C caused an increase of aggregation number and a concomitant decrease of micellar hydration in both irradiated and nonirradiated systems. The relevance of these changes in micellar properties to the thermal gelation of T908 is discussed.

Introduction

The poloxamines are block copolymers prepared by the polycondensation of propylene oxide and ethylene oxide on ethylenediamine. Their general structure is



$$\begin{matrix} H(C_2H_4O)_y(C_3H_6O)_x \\ H(C_2H_4O)_y(C_3H_6O)_x \end{matrix} \!\!>\! NCH_2CH_2N \!<\!\! \begin{matrix} (C_3H_6O)_x(C_2H_4O)_yH \\ (C_3H_6O)_x(C_2H_4O)_yH \end{matrix}$$

In common with other poly(oxyethylene)-poly(oxypropylene) block copolymers, high molecular weight members of the series form thermally reversible gels in aqueous solution. The most widely studied copolymer which exhibits reversible gelation is the poloxamer, Pluronic F127. Solutions of this poloxamer with concentrations greater than 20% w/v are reversibly transformed from low viscosity transparent solutions to gels on warming from ambient to body temperature. The potential for the use of gels of this nature in the controlled release of drugs has led to investigations of the gelation process (Miller and Drabik, 1984; Vadnere et al., 1984; Attwood et al., 1985, 1987; Gilber et al., 1987) and of the controlled release of drugs incorporated into the gel network (Chen-Chow and Frank, 1981; Miller and Donovan, 1982; Miyazaki et al., 1984; Collett et al., 1985; Gilbert et al., 1986; Tait et al., 1987).

In contrast to the extensive published work on the association characteristics of the poloxamer

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series of block copolymers, very little has been reported on the properties of the poloxamine series. Sheth (1967) has determined a critical micelle concentration (CMC) of 0.06 g dl^{-1} at 25° C for Synperonic (Tetronic) T908, the poloxamine used in the present study. Synperonic (Tetronic) T707 has also been shown to exhibit micelle formation commencing at a CMC of 0.005 g dl^{-1} at 25° C (Schmolka and Raymond, 1965). In this investigation, we report a detailed study of the association characteristics of T908 in aqueous solution and of the changes which occur in the micellar properties during the onset of gelation.

We have previously shown (Attwood and co-workers, 1987) that exposure of solutions of the poloxamer, Pluronic F127, to γ-irradiation induced gelation at lower concentrations than in nonirradiated systems. Al Saden and co-workers (1981) have demonstrated that γ-irradiation does not cause scission of the poly(oxyethylene) chains in aqueous solutions of poloxamers when the chain length exceeds approx. 50 ethylene oxide units per hydrophilic chain. These workers have successfully induced the gelation of solutions of Pluronics F68, F87 and F88 by exposure to γ-irradiation. In this study we have investigated the effect of graded doses of γ-irradiation on the micellization of T908 and on the temperature-induced changes in properties which lead to the eventual gelation of these solutions.

Materials and Methods

Materials

Synperonic T908 was a gift from ICI plc and was used as received. T908 is a poly(oxyethylene)-poly(oxypropylene) block copolymer (poloxamine) containing approx. 80% oxyethylene with a nominal molecular weight of 2.5×10^4. Synperonic T908 has a similar structure to Tetronic T908 (BASF, Wyandotte). In view of possible inter-batch variations of properties, all measurements were carried out on solutions prepared from the same batch.

Methods

Irradiation procedure. 30% w/w solutions of T908 were prepared at 5° C in distilled water and saturated with nitrous oxide. This agent is a scavenger of hydrated electrons produced by the irradiation of water thereby increasing the efficiency of γ-irradiation. The presence of this agent is known to enhance crosslinking of poly(oxyethylene) chains (Stafford, 1970). Vials containing T908 solutions were irradiated at ambient temperatures in a 2000 Ci ^{60}Co source at a dose rate of 0.5 Mrad h^{-1}. Physico-chemical measurements were performed on solutions prepared by dilution of these irradiated samples.

Photon correlation spectroscopy (PCS). The diffusion coefficients of the micellar species were measured using a Malvern K7027 correlator with 26 delay channels arranged in geometric progression, in conjunction with a 2 W argon ion laser at 488 nm. Solutions were clarified by ultrafiltration through 0.22 μm Millipore filters and measurements were made at the specified temperatures ±0.1° C.

Light scattering measurements. Light scattering was monitored using a Fica 42000 photogoniodiffusometer at a wavelength of 546 nm. Temperature control was to within ±0.1° C. Solutions were clarified by ultrafiltration through 0.22 μm Millipore filters. The refractive index increments, dn/dC, of the micellar species were determined using an Abbé 60/ED precision refractometer. No detectable change of dn/dC with irradiation dose or temperature change was observed and a mean value of 0.128 ml g^{-1} was used throughout this study.

Surface tension measurements. Determination of the surface tension was performed by the Wilhelmy plate technique using a thin, rectangular glass plate suspended from a calibrated torsion balance. The temperature was controlled to within 0.1° C of the specified value and precautions were taken to minimize evaporation of the solutions during measurement. The usual precautions were taken to ensure cleanliness and the accuracy of measurement was checked by frequent determinations on pure water. A preliminary investigation of the ageing effects showed that between 4 and 6 h were required for the attainment of consistent readings and this time interval was adopted for all measurements.

Viscosity measurements. Viscosity measurements were carried out using a suspended-level viscometer at the specified temperatures ±0.01 °C. Partial specific volumes were calculated from density measurements made using a digital density meter (Paar DMA 02C).

Results

Influence of irradiation on micellar and gelation properties at 40 °C

Fig. 1 shows surface tension, γ, at 40 °C as a function of log C (where C is the % weight concentration) for nonirradiated solutions of T908 and for solutions subjected to an irradiation dose of 1.2 Mrad. The data for both of these systems were superimposable within the limits of error of measurement, showing that the irradiation had no detectable effect on the surface properties. A sharp inflection point is noted at the critical micelle concentration (CMC) and the constant surface tension above the CMC indicates the formation of a full Gibbs monolayer. The area per molecule, A, was calculated from the limiting gradient of the plot immediately below the CMC using $A = 1/\Gamma N_A$ where N_A is Avogadro's number and Γ is the surface excess concentration as determined from the Gibbs adsorption isotherm,

$$\Gamma = (1/2.3RT)(\mathrm{d}\gamma/\mathrm{d}\log C) \qquad (1)$$

The values of CMC and A are given in Table 1. The CMC was considered to be sufficiently low for data from the other physicochemical techniques used in this study to be extrapolated to zero concentration without significant error.

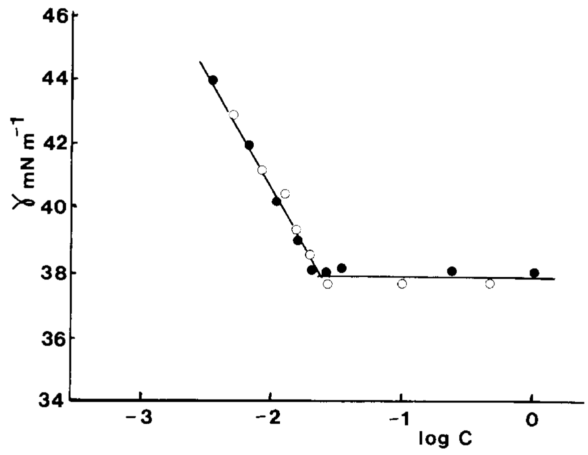

Fig. 1. Surface tension, γ, as a function of log C (% w/w concentration) at 40 °C for (●) nonirradiated and (○) irradiated (1.2 Mrad) solutions of Synperonic T908.

The concentration dependence of the diffusion coefficient of the micelles, as determined by PCS, in solutions exposed to graded doses of irradiation is shown in Fig. 2. The plots were linear over the low concentration region (up to about 2% w/w) indicating constant micelle size in dilute solution. Extrapolation to infinite dilution yielded the values of the limiting diffusion coefficient, D_0, listed in Table 1. The decay constant of the autocorrelation function was shown to be a linear function of $\sin^2\theta/2$ (where θ is the scattering angle) over this low concentration range, indicating micellar sphericity. Accordingly, the hydrodynamic radius, r_h, was calculated from the Stokes-Einstein equation in the form,

$$D_0 = kT/6\pi\eta_0 r_h, \qquad (2)$$

where η_0 is the solvent viscosity, k is Boltzmann's

TABLE 1

Effect of radiation dose on the micellar properties of Synperonic T908 in aqueous solution at 40 °C

Radiation dose (Mrad)	CMC (% w/w)	A (nm^2)	D_0 ($\times 10^{11}$ m^2 s^{-1})	r_h (nm)	N	$[\eta]$	δ (g H$_2$O/g T908)
0	0.020	1.1	2.74	12.8	3.2	25.8	9.4
0.2	–	–	–	–	3.2	27.5	10.1
0.4	–	–	2.62	13.4	3.2	28.8	10.5
0.8	–	–	2.51	14.0	3.2	31.0	11.4
1.2	0.020	1.1	2.31	15.2	3.2	34.0	12.6

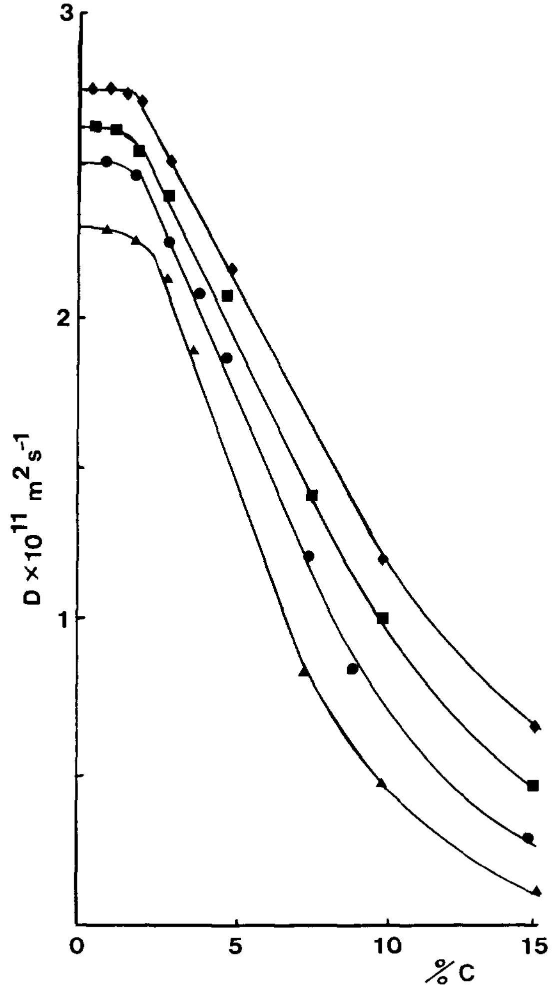

Fig. 2. Variation of diffusion coefficient, D, with concentration C at 40 °C for solutions of Synperonic T908 given doses of γ radiation of (◆) 0, (■) 0.4, (●) 0.8 and (▲) 1.2 Mrad.

constant and T is the absolute temperature. Table 1 shows a progressive increase of micelle size with increase of irradiation dose.

The time-average light scattering data are plotted in Fig. 3 as S_{90} vs C, where S_{90} is the observed ratio of the intensity of light scattered from the solution at an angle of 90 °, to that from a calibrated standard. The plots were linear up to concentrations of 1% w/w, supporting the conclusions from the PCS data that micellar size is concentration-independent in dilute solution. Fig. 3 shows that light scattering data from solutions subjected to a range of irradiation doses were superimposable indicating that γ-irradiation was not significantly affecting the aggregation number of the micelles in these systems (Table 1). From the combination of PCS and light scattering data it was inferred that the increase of hydrodynamic diameter with increase of irradiation dose was due entirely to an increase in micellar hydration. The viscosity results (see below) were supportive of this conclusion.

Preliminary measurements using a rotational viscometer demonstrated Newtonian flow properties for dilute solutions of T908, and consequently capillary viscometry was used to determine the viscometric properties of these solutions. Fig. 4 shows an increase of intrinsic viscosity $[\eta]$ with increase of irradiation dose, as determined by extrapolation of viscosity data plotted according to

$$\eta_{sp}/C = [\eta] + K_H[\eta^2]C \qquad (3)$$

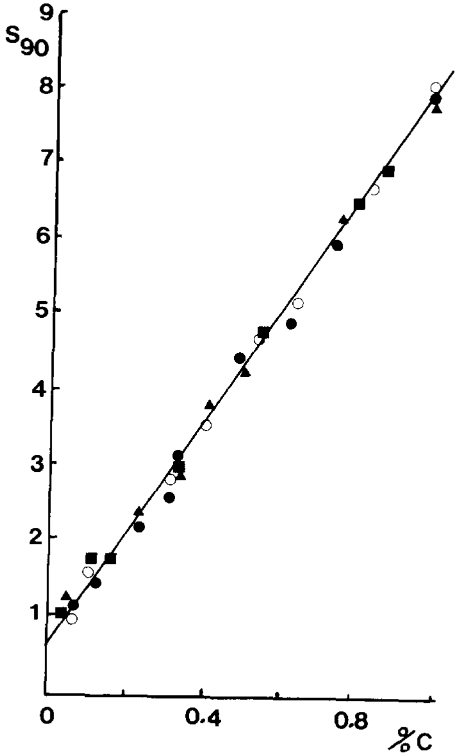

Fig. 3. Light scattering ratio, S_{90}, as a function of concentration C at 40 °C for solutions of Synperonic T908 given doses of γ radiation of (●) 0, (▲) 0.4, (■) 0.8 and (○) 1.2 Mrad.

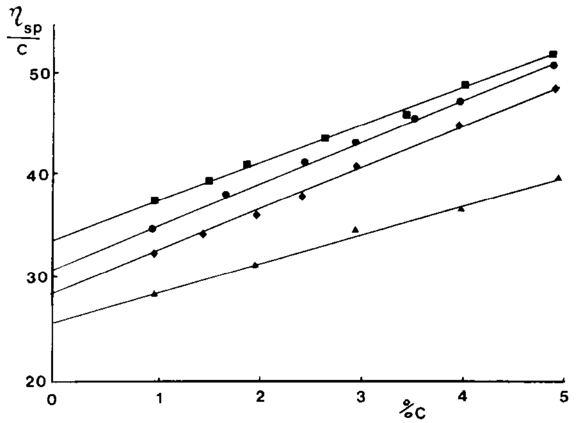

Fig. 4. Concentration dependence of reduced viscosity at 40 ° C for solutions of Synperonic T908 given doses of γ radiation of (▲) 0, (◆) 0.4, (●) 0.8 and (■) 1.2 Mrad.

where η_{sp} is the specific viscosity and K_H is Huggin's constant. Micellar hydration, δ, was calculated using the Oncley equation

$$[\eta] = \nu(\bar{v} + \delta V^0) \tag{4}$$

A value of 2.5 was assigned to the viscosity increment ν assuming micellar sphericity and the specific volume of water, V^0, was assumed to be unity. The partial specific volume, $\bar{v}$, was determined from the gradients of plots of density vs concentration in the usual way. Hydration levels were higher than could be accounted for by hydrogen bonding to the ether oxygens of the polyoxyethylene chains and indicated considerable mechanical entrapment of water in the palisade layer of the micelles. Table 1 shows an increase of hydration with increase of irradiation dose as predicted from the PCS and light scattering data.

The influence of graded doses of radiation on the gelation of the solutions may be deduced from the PCS data at high solution concentration. Fig. 2 shows pronounced decreases in D with concentration increase for each system indicative of an increase of micelle size and/or interparticle interaction. If the data are interpreted entirely in terms of changes in the size of the spherical micelles, then Fig. 5 shows that the sudden increases of size, which lead to the eventual gelation of the solutions, occurred at progressively lower concentrations as the irradiation dose was increase.

Analysis of the polydispersity of micelle size was performed by the method of cumulants (Koppel, 1972) and by the exponential sampling method of Ostrowsky and co-workers (1981). Values of the polydispersity index, Q, from cumulant analysis of nonirradiated solutions of 2, 5 and 10% w/w were 0.14, 0.23 and 0.30, respectively, indicating increase in polydispersity of micelle size with increase in concentration. Similar results were obtained for nonirradiated solutions. The size distri-

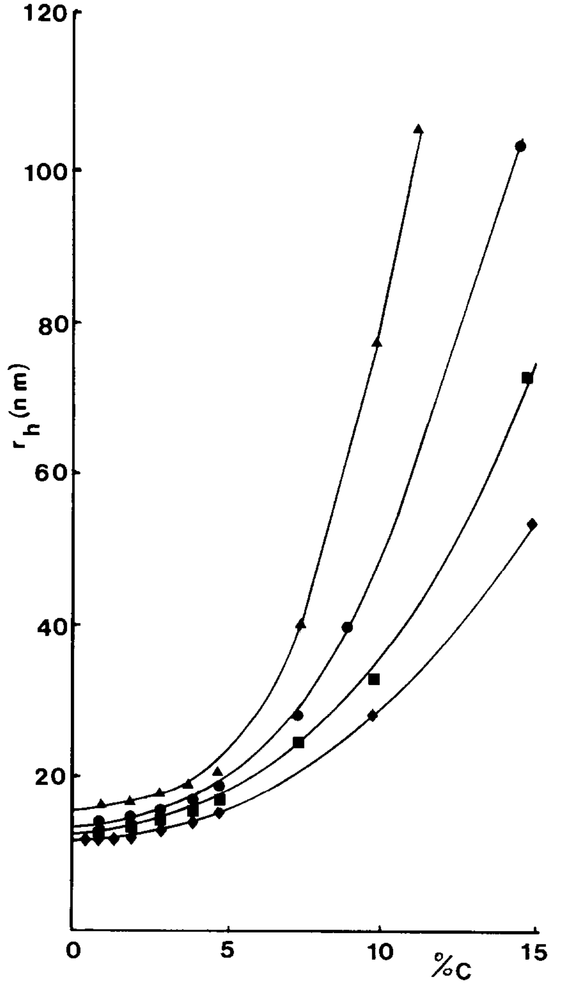

Fig. 5. Apparent hydrodynamic radius r_h as a function of concentration at 40 ° C for Synperonic T908 solutions given doses of γ radiation of (◆) 0, (■) 0.4, (●) 0.8 and (▲) 1.2 Mrad.

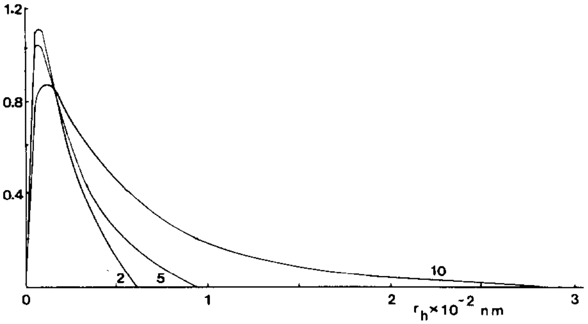

Fig. 6. Micellar size distribution curves for 2, 5 and 10% w/w Synperonic T908 in water at 40 °C.

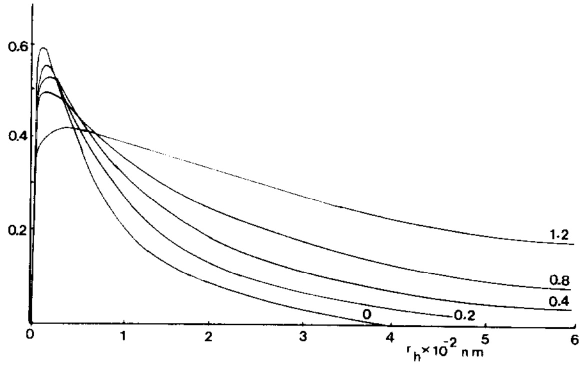

Fig. 7. Micellar size distribution curves for 10% w/w Synperonic T908 at 40%, given the doses of γ radiation indicated.

bution curves from the exponential sampling method showed a marked broadening with increase of concentration (Fig. 6) which supports the conclusions from the cumulant analysis of the data. The influence of irradiation dose on the polydispersity at a fixed concentration (10%) is clearly seen from the Q values and half peak widths from size distribution curves listed in Table 2. Both methods of size analysis showed progressive increases of the polydispersity of micelle size with increase of irradiation dose.

Influence of temperature change on the micellar and gelation properties of irradiated and nonirradiated solutions

Fig. 8 shows a decrease of CMC and increase of surface activity following temperature increase over the range 30–50 °C for nonirradiated solutions, but no significant change in the area per molecule. The effect of temperature change on the surface activity of irradiated solutions was not examined, although it should be noted that the surface tension data at 40 °C for irradiated and nonirradiated solutions were superimposable (see Fig. 1).

Limiting diffusion coefficients, obtained by extrapolation of the linear portions of D vs C plots (Fig. 9) over the concentration region $C \leqslant 3\%$ w/w, increased progressively with temperature increase for both irradiated and nonirradiated solutions (Table 3). Calculations of micellar size by the application of Eqn. 2 to the diffusion data showed that temperature increase had only a minimal effect on the hydrated radius in nonirradiated

TABLE 2

Effect of radiation dose on the polydispersity of micellar size for 10% w/w Synperonic T908 at 40 °C

Radiation dose (Mrad)	Q [a]	Half peak width [b] (nm)
0	0.30	100
0.2	0.32	200
0.4	0.34	275
0.8	0.39	355
1.2	0.45	1030

[a] Polydispersity index from cumulants analysis.
[b] Half peak width of size distribution curve.

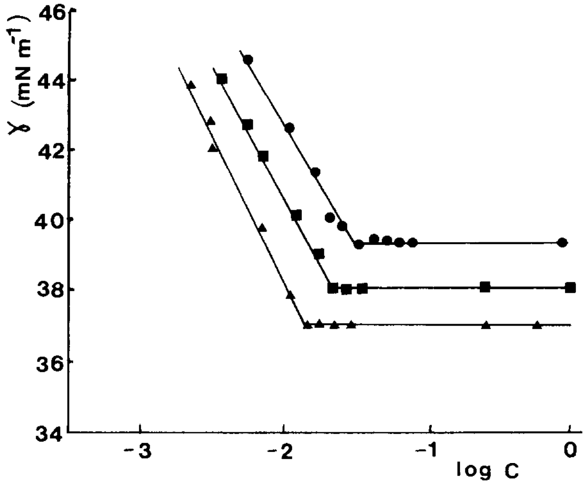

Fig. 8. Surface tension, γ, as a function of log C (% w/w) for solutions of Synperonic T908 at (●) 30, (■) 40 and (▲) 50 °C.

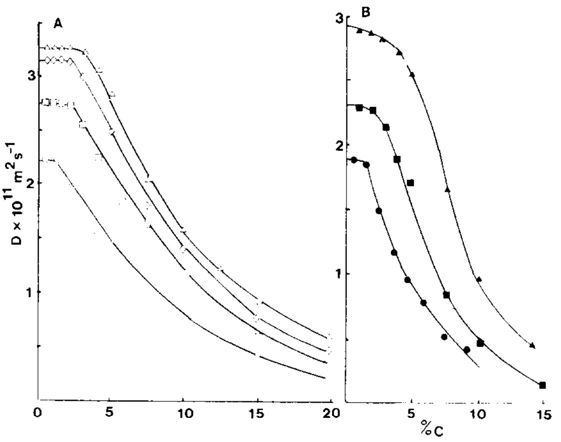

Fig. 9. Variation of diffusion coefficient, D, with concentration, C, for solutions of Synperonic T908 at (○) 30, (□) 40, (◇) 45 and (△) 50 °C. (A) Nonirradiated solutions. (B) Solutions given a dose of γ radiation of 1.2 Mrad.

solutions (Table 3) whilst causing a significant decrease of r_h in solutions receiving a 1.2 Mrad dose.

Any changes in r_h were not a consequence of corresponding changes in the aggregation number of the micelles. Values of N derived from the linear S_{90}-C plots of Fig. 10 increased with increasing temperature, i.e. the tendency was for an increase rather than a decrease of micelle size with increasing temperatures. Light scattering data for irradiated and nonirradiated solutions were superimposable at each temperature, supporting the conclusion above that the irradiation process did not affect the aggregation number.

Examination of light scattering and PCS results suggests that the temperature-induced decrease of micellar size must be a consequence of micellar dehydration with temperature increase. More direct evidence for this was obtained from viscometric measurements. Fig. 11 shows progressive de-

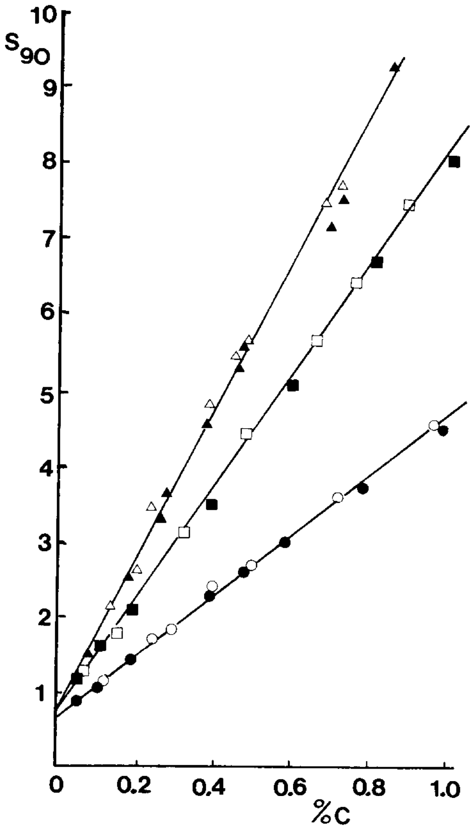

Fig. 10. Light scattering ratio, S_{90}, as a function of concentration, C, for solutions of Synperonic T908 at (○) 30, (□) 40 and (△) 50 °C. Open symbols denote nonirradiated solutions; closed symbols denote solutions given a dose of γ radiation of 1.2 Mrad.

TABLE 3

Effect of temperature on micellar properties of nonirradiated and irradiated (1.2 Mrad) solutions of Synperonic T908

Temperature (°C)	CMC (% w/w)	A (nm^2)	D_0 ($\times 10^{11}$ m^2 s^{-1})	r_h (nm)	N	$[\eta]$	δ (g H_2O/g T908)
Nonirradiated							
30	0.028	1.3	2.26	12.3	1.7	27.4	10.0
40	0.020	1.1	2.74	12.8	3.2	25.8	9.4
50	0.013	1.2	3.34	13.0	4.2	23.0	8.2
Irradiated							
30	–	–	1.77	15.7	1.7	36.1	13.5
40	0.020	1.1	2.31	15.2	3.2	34.0	12.6
50	–	–	2.95	14.7	4.2	32.0	11.8

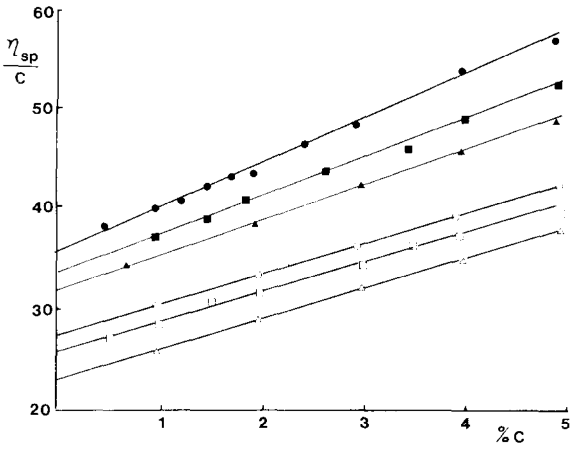

Fig. 11. Concentration dependence of reduced viscosity for solutions of Synperonic T908 at (○) 30, (□) 40 and (△) 50 °C. Open symbols denote nonirradiated solutions; closed symbols denote solutions given a dose of γ radiation of 1.2 Mrad.

creases of intrinsic viscosity with temperature increase for both irradiated and nonirradiated systems. Interpretation of these changes entirely in terms of hydration changes, i.e. assuming that micellar sphericity was retained at all temperatures, led to the values of δ given in Table 3. In the case of the nonirradiated systems, it is clear that the decrease of hydration was counterbalanced by the increase of aggregation number such that the hydrodynamic diameter was not significantly influenced by temperature change. With the more heavily hydrated micelles in the irradiated systems, the dehydration process was such that there was an overall decrease of micellar diameter, despite the increased aggregation numbers.

It is clear from Fig. 12 that the increases of micelle diameter and/or interaction which reflect the onset of gelation of the systems were more pronounced and occurred at lower solution concentrations with the irradiated systems at each temperature.

Discussion

The examination of changes in the properties of aqueous solutions of the poloxamines which occur prior to their gelation enables the mechanism of gelation to be elucidated. The increase in micellar size and polydispersity with increase of solution concentration is a consequence of increased interaction between poly(oxyethylene) chains of adjacent micelles which, as a result of their dehydration at elevated temperature, experience increased friction. At high solution concentrations these interactions are such that multimicellar units are formed, resulting eventually in the formation of a micellar gel. It is apparent that the gelation of this poloxamine occurs by a mechanism similar to that proposed for the poloxamer, Pluronic F127 (Attwood and co-workers, 1985).

This investigation has shown that the mechanism of gel formation in irradiated gels follows a

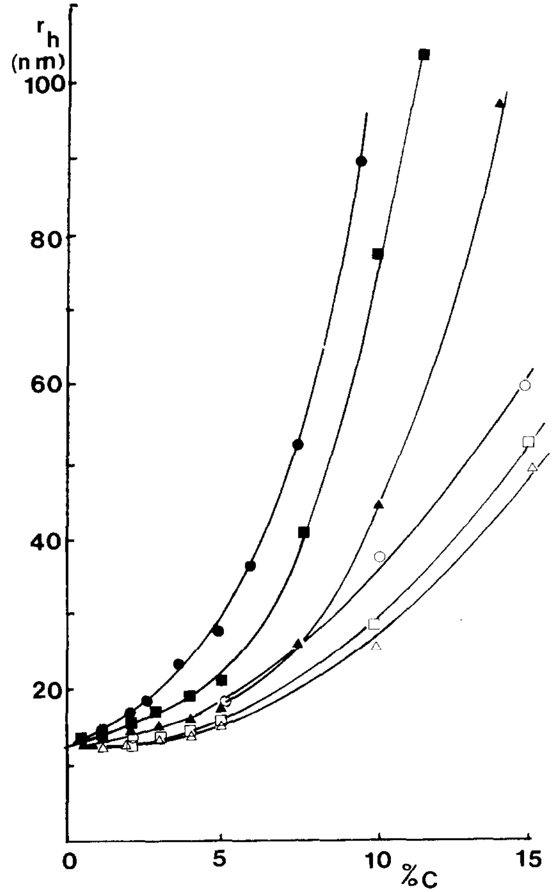

Fig. 12. Apparent hydrodynamic radius, r_h, as a function of concentration for Synperonic T908 solutions at (○) 30, (□) 40 and (△) 50 °C. Open symbols denote nonirradiated solutions; closed symbols denote solutions given a dose of γ radiation of 1.2 Mrad.

similar pattern, but that the changes in properties which signal the onset of gelation occur at progressively lower solution concentrations as the irradiation dose is increased up to 1.2 Mrad. This promotion of gelation by the γ-irradiation is presumably a consequence of induced crosslinking of the hydrophilic chains of adjacent micelles. Indeed, the increased hydration of the micelles in the irradiated systems suggests changes in configuration of the poly(oxyethylene) chains or the formation of intramicellar links such that the extent of water entrapment is increased. In this respect, it is of interest to note the work of Stafford (1970) and Guven and Senvar (1979) which shows that, in the absence of oxygen, concentrated aqueous solutions of poly(oxyethylene) glycols crosslink to form gels after exposure to γ-irradiation. The radiation dosage used in this study was restricted such that the gels which formed at high solution concentration still retained their reversibility, i.e. any induced cross-linkage was not permanent and the gels reverted to isotropic micellar solutions on cooling.

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