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Influence of gamma irradiation on the rheological properties of gels of the poloxamine, Synperonic T908

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Summary

Aqueous solutions of the poloxamine, Synperonic (Tetronic) T908 formed thermally reversible gels at concentrations $\geqslant$ 30% w/w, which exhibited plastic flow properties at temperatures exceeding 27 °C. The yield stress increased with increasing concentration of T908 over the range 30–40% w/w and with increase of temperature between 27 and 42 °C. Gamma irradiation of the gels produced a progressive increase of yield stress with radiation dose up to 0.4 Mrad. At radiation doses exceeding 0.8 Mrad, flow was pseudoplastic and conformed to the empirical relationship, log(shear stress) = log $K + n$ log(shear rate). Values of the flow index, n, were < 1 indicating shear thinning behaviour. The consistency index, K, increased with increase of temperature between 27 and 42 °C, with concentration over the range 30–40% w/w and with radiation dose up to 2.4 Mrad.

Introduction

Synperonic T908 is a water-soluble block copolymer of poly(oxyethylene)-poly(oxypropylene) with a nominal molecular weight of 2.5×10^4. In a previous study (Attwood et al., 1990) it was shown that this poloxamine forms micelles in aqueous solution over the temperature range 30–50 °C. Gelation occurs in solutions of concentration greater than 30% due to an increase of micelle size and intermicellar interaction with temperature increase, accompanied by a corresponding desolvation of the poly(oxyethylene) chains which enhances their entanglement. Exposure of solutions of T908 to increasing doses of gamma irradiation up to 1.2 Mrad was shown to induce gelation at progressively lower concentrations. The thermally reversible characteristics and solubilization capacities of block copolymer gels have led to an interest in their potential application in the controlled release of drugs (Chen-Chow and Frank, 1981; Miller and Donovan, 1982; Miyazaki et al., 1984, 1986, 1987; Collett et al., 1985; Gilbert et al., 1986; Tait et al., 1987). The most widely studied block copolymer in this respect is the poloxamer Pluronic F127. The rheological properties of gels of this copolymer have been studied by several workers. Lenaerts et al. (1987) have reported pseudoplastic flow properties for 30% gels of F127 at 14 °C and a change to plastic flow with increase of temperature to 24 °C. Miller and Drabik (1984) have noted shear thinning flow characteristics for a series of poloxamers including F127 (poloxamer 407).

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In this investigation we report a study of the rheological properties of gels of Synperonic T908 over a range of concentrations and temperature. In view of the potential use of gamma irradiation in the sterilization of parenteral dosage forms, we have investigated the influence of graded doses of gamma radiation on the flow characteristics.

Materials and Methods

Materials

Synperonic T908 (ICI Chemicals and Polymers Ltd) was used as received. This poly(oxyethylene)-poly(oxypropylene) block copolymer (poloxamine) contains approx. 80% oxyethylene and has a structure similar to that of Tetronic T908 (BASF Wyandotte)

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

Methods

Irradiation procedure Solutions of T908 of the required concentration were prepared in distilled water at 5 °C, saturated with nitrous oxide (a scavenger of hydrated electrons) and irradiated in anoxia at ambient temperature in a 2000 Ci ^{60}Co source at a dose rate of 0.5 Mrad h^{-1}.

Viscometric measurements Rheological studies were performed using a rotating cylinder viscometer (Rheomat 135, Contraves) at the specified temperatures ±0.1 °C. Measurements were conducted at shear rates increasing and subsequently decreasing over the range 1–10 s^{-1}. Samples were sheared for 6 s at each shear rate. Preliminary measurements showed no dependence of viscosity on time of shearing with any of the gels.

Results

Effect of gamma irradiation on the rheological properties

Fig. 1 shows rheograms for solutions of T908 over the concentration range 25–40% w/w at

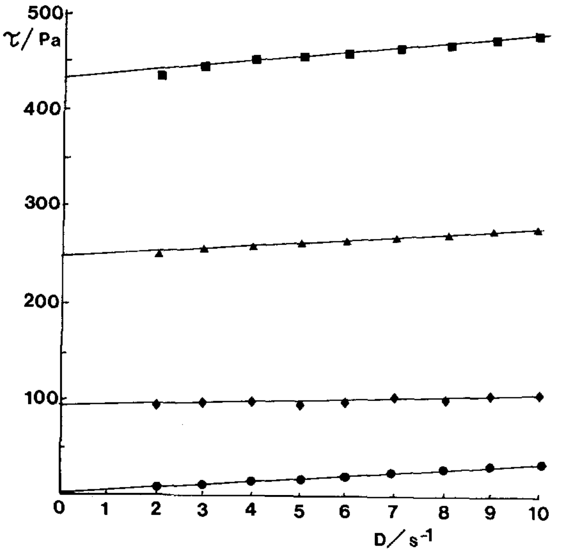

Fig. 1. Rheograms for nonirradiated gels of Synperonic T908 of concentration: (●) 25, (◆) 30, (▲) 35 and (■) 40% w/w at 37 °C.

37 °C. The linearity between shear stress, τ and shear rate, D for the 25% w/w solution, with data extrapolating through the origin, denotes Newtonian flow characteristics. At higher concentrations, gelation of the solutions caused a change to plastic flow. The viscosity was high at low shear rates and the data extrapolated to a critical shear

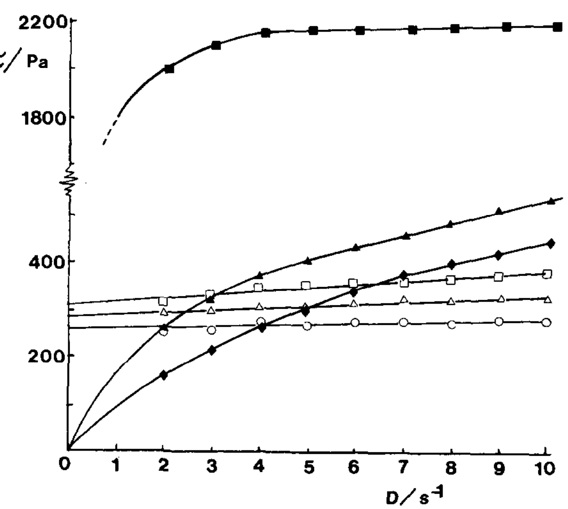

Fig. 2. Rheograms at 37 °C for 35% w/w gels of Synperonic T908 after irradiation with doses of: (○) 0, (△) 0.2, (□) 0.4, (◆) 0.8, (▲) 1.2 and (■) 2.4 Mrad.

stress, the yield stress, which increased with increasing concentration in the following way:

Concentration (% w/w)	30	35	40
Yield stress (Pa)	95	250	434

After yielding, the shear stress was a linear function of shear rate, i.e. the systems were Bingham fluids.

The flow behaviour of gels after irradiation with doses of 0.2 and 0.4 Mrad was similar to that noted for the nonirradiated systems. Fig. 2 shows representative plots for a 35% w/w gel at 37 °C. Flow did not commence until a critical shear stress was exceeded, the value of which increased with increasing radiation dose up to 0.4 Mrad as follows:

Radiation dose (Mrad)	0	0.2	0.4
Yield stress (Pa)	250	288	309

In contrast, after irradiation with doses of 0.8–2.4 Mrad a continuous increase of shear stress was seen with no apparent yield stress, i.e. the gel exhibited pseudoplastic flow behaviour. Fig. 3 shows that these systems obeyed the empirical relationship

$$\log \tau = \log K + n \log D \quad (1)$$

where K is the consistency index and n the flow index. Values of n were less than 1 indicating shear thinning properties (see Table 1). Fig. 4 shows the data for the 35% w/w gels at 37 °C

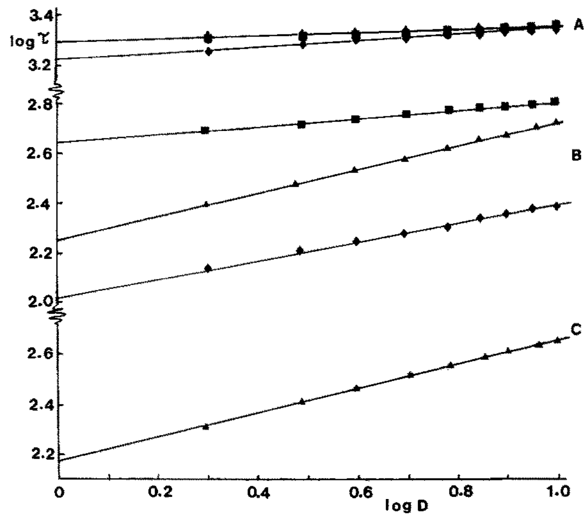

Fig. 3. Viscosity data at 37 °C plotted in accordance with Eqn 1 for gels of Synperonic T908 of concentration: (◆) 30, (▲) 35 and (■) 40% w/w after irradiating with doses of (A) 2.4, (B), 1.2 and (C) 0.8 Mrad.

plotted as apparent viscosity against shear rate and clearly demonstrates their shear thinning behaviour.

The concentration dependence of the flow properties of gels receiving radiation doses of 1.2 and 2.4 Mrad was examined. An interesting difference between the behaviour of these two irradiated gels may be seen in Fig. 3. The log K and n values derived from plots of log τ against log D for gels receiving 2.4 Mrad were almost identical over the concentration range 30–40% w/w, indicating no appreciable dependency of flow be-

TABLE 1

Rheological properties of Synperonic T908 gels (from Eqn 1) as a function of temperature, concentration and radiation dose

Radiation dose (Mrad)	Concn (% w/w)	n				log K			
		27 °C	32 °C	37 °C	42 °C	27 °C	32 °C	37 °C	42 °C
0.8	30								
	35	0.50	0.47	0.46	0.47	2.03	2.12	2.18	2.20
	40								
1.2	30	0.42	0.37	0.37	0.39	1.81	1.96	2.03	2.09
	35	0.53	0.50	0.46	0.43	2.03	2.15	2.26	2.35
	40	0.41	0.24	0.15	0.16	2.24	2.52	2.65	2.71
2.4	30	0.11	0.09	0.15	0.00	3.12	3.18	3.21	3.34
	35	0.13	0.13	0.05	0.00	3.15	3.21	3.30	3.34
	40	0.13	0.10	0.00	0.00	3.17	3.24	3.34	3.32

haviour on concentration. This behaviour was in marked contrast to that observed with gels receiving 1.2 Mrad, which showed an increase of consistency index with concentration (Table 1) similar to that noted with the nonirradiated system.

Effect of temperature on rheological properties

Plastic flow was observed at all temperatures over the range 27–42° C, for 35% w/w gels (Fig. 5), with a progressive increase of yield stress with temperature as follows:

Temperature (° C)	27	32	37	42
Yield stress (Pa)	204	219	250	270

Rheograms for 30, 35 and 40% w/w gels given doses of 0.8–2.4 Mrad showed pseudoplastic flow properties at each temperature. Fig. 5 shows representative plots for a 35% w/w gel receiving 1.2 Mrad. Shear stress conformed to Eqn 1 (see Fig. 6) with the values of log K and n given in Table

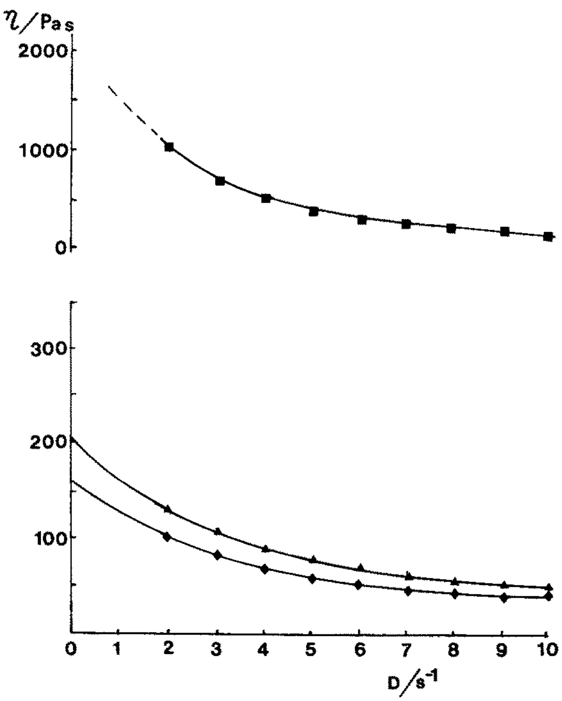

Fig. 4. Apparent viscosity, η, as a function of shear rate at 37° C for 35% w/w gels of Synperonic T908 after irradiating with doses of: (◆) 0.8, (▲) 1.2 and (■) 2.4 Mrad.

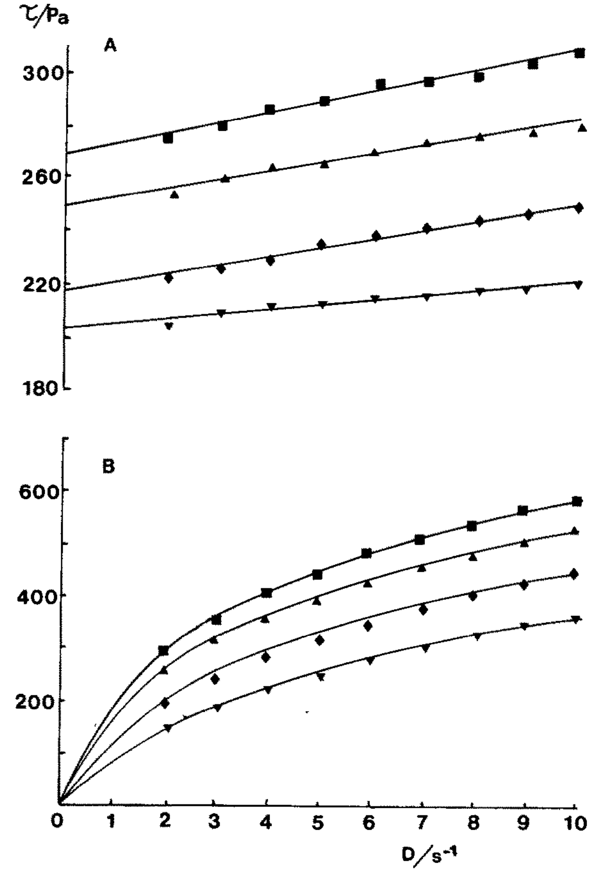

Fig. 5. Rheograms for 35% w/w gels of Synperonic T908 at temperatures of: (▼) 27, (◆) 32, (▲) 37 and (■) 42° C. (A) Nonirradiated gels. (B) Gels irradiated with a dose of 1.2 Mrad.

1. Increase of temperature caused a progressive increase of log K for the systems given doses of 0.8 and 1.2 Mrad, but had a less pronounced effect on the 2.4 Mrad system. Similarly, the increase of log K with concentration for the gels irradiated with a dose of 1.2 Mrad at each temperature was more marked than with gels irradiated with 2.4 Mrad.

Discussion

The measurements of shear stress as a continuous function of shear rate for gels of Synperonic T908 have provided an insight into the mechanism

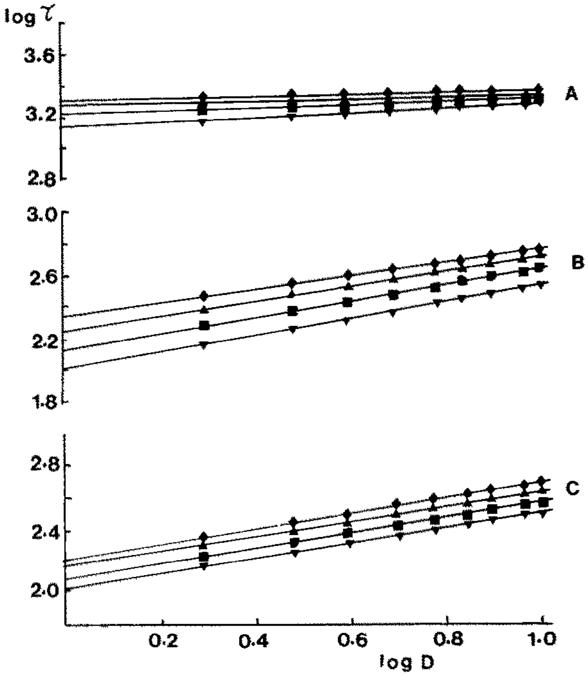

Fig. 6. Viscosity data plotted in accordance with Eqn 1 for 35% w/w Synperonic T908 gels at temperatures of: (▼) 27, (■) 32, (▲) 37 and (◆) 42°C after irradiating with doses of (A) 2.4, (B) 1.2 and (C) 0.8 Mrad.

of gelation of these systems and the influence of γ irradiation on the gelation process. The change of flow properties from Newtonian to non-Newtonian flow when the concentration of the Synperonic/water systems exceeded 25% w/w (Fig. 1) corresponds to the onset of gel formation. We have shown from previous studies of the changes in the properties of aqueous solutions of Synperonic T908 (Attwood et al., 1990) that gelation is a consequence of an increase of micelle size and intermicellar interaction with temperature increase, accompanied by corresponding temperature-induced dehydration of the micelles. As a consequence, the desolvated poly(oxyethylene) chains of adjacent micelles in concentrated solutions interact and interlink the micelles as a reversible network. These changes in micellar properties occur gradually with concentration and temperature change and hence would be expected to cause similar continuous changes in the rheological properties, rather than an abrupt sol-gel transition. The concentration- and temperature-induced changes in flow properties shown in Figs 1 and 5, respectively, support the hypothesis for the mechanism of gelation previously proposed. Increase of concentration results in an increase of yield stress since the greater number of possible crosslinks between adjacent micelles causes a stronger gel network. Similarly, temperature increase results in increased yield stress due to increased dehydration of the poly(oxyethylene) chains, which allows more effective crosslinking when chains of adjacent micelles come into contact.

Similar continuous changes in the viscosity of solutions of the poloxamer, Pluronic F127, which exhibits a similar gelation mechanism to that of T908 (Rassing et al., 1984; Attwood et al., 1985, 1987; Gilbert et al., 1987) have been reported by Lenaerts et al. (1987), in contrast to the abrupt sol-gel transition temperatures reported by Vadnere et al. (1984) from calorimetric measurements. Lenaerts et al. (1987) have demonstrated plastic flow properties for 30% solutions of Pluronic F127 at temperatures above 24°C, in agreement with the findings of this present study.

Our previous studies (Attwood et al., 1990) have shown that γ irradiation of solutions of T908 caused gelation at lower concentrations than in nonirradiated systems by inducing the formation of crosslinks between adjacent poly(oxyethylene) chains. This present study has shown that such changes in intermicellar interaction cause a pronounced effect on the flow properties of the gel, with a transition from plastic to pseudoplastic flow occurring when the radiation dose exceeded 0.4 Mrad. Increase of radiation dose caused an increase of gel strength of each type of system. Thus, the yield stress of the plastic systems and the consistency index of the pseudoplastic system both increased with radiation dose at constant temperature and concentration.

The mechanism of gelation in the irradiated systems was previously shown (Attwood et al., 1990) to be the same as that in the nonirradiated solutions. The increased gel strength with increase of temperature and concentration as shown by the values of log K for the 1.2 Mrad systems (Table 1) support this conclusion. That such changes are not apparent in the 2.4 Mrad systems over similar temperature and concentration range suggests that the gels produced under such conditions have attained limiting properties.

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