

# Ultrasonic velocity and light-scattering studies on the polyoxyethylene–polyoxypropylene copolymer Pluronic F127 in aqueous solution

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## Summary

Ultrasonic velocity and light-scattering measurements on aqueous solutions of the ABA polyoxyethylene–polyoxypropylene block copolymer, Pluronic F127, have clearly indicated a micellar mode of association over the temperature range 10–40°C. The extent of association was limited below 25°C but increased markedly at higher temperatures giving micelles with a mean weight-average aggregation number of 44 at 40°C. A pronounced decrease in the critical micelle concentration accompanied the micellar enlargement. Aggregates were asymmetric at low temperatures but increased in symmetry with temperature increase becoming spheroidal above 25°C.

A theoretical treatment of the concentration-dependent changes in ultrasonic velocity is proposed from which information concerning the volume change on micellization may be obtained. Micellization of F127 over the temperature range 20–30°C has been shown to be associated with a very small change in the molar volume of the monomers and this volume change decreased with increases in temperature to the extent of 2%/°C. The temperature-dependent changes in micellar properties have been related to the reversible thermal gelation of this block copolymer.

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## Introduction

Polyoxyethylene–polyoxypropylene–polyoxyethylene (ABA) type block copolymers are widely used in pharmaceutical systems as wetting and solubilizing agents (Schmolka, 1977). Pluronic F127 is of particular interest since concentrated solutions (20–30%) of the copolymer are transformed from low viscosity transparent solutions to solid gels on heating from 5°C to room temperature or body temperature. The potential of these gels as drug delivery systems has been investigated (Chen-Chow, 1980; Chen-Chow and Frank, 1981). These authors have presented evidence from X-ray diffraction, thermal polarizing microscopy, and differential scanning calorimetric techniques that the gels are micellar in nature being constructed from a cubic orientation of micellar subunits. It is consequently of interest to examine any changes which might occur in solutions of F127 over this temperature range so that the gelation process might be more fully understood.

This paper reports the results of an examination of dilute solutions of the copolymer using light-scattering and ultrasonic velocity techniques. The latter technique has been previously used as a tool for studying polymer solutions (Rassing, 1971), sol–gel transitions (Dela and Rassing, 1978) and diffusion of drugs inside polymer matrices (Dela et al., 1979; Attwood et al., 1981). Our previously reported theoretical treatment of ultrasonic velocity is now extended to give information on the volume change for a micellization process and has been applied to the F127 system.

## Theory

It is well known that the variation of the ultrasonic velocity of micellar solutions with overall concentration is approximately linear both above and below the critical micelle concentration (cmc) with a pronounced inflection at the cmc (Rassing et al., 1974). In this paper our previously reported theoretical treatment of the ultrasonic velocity (Attwood et al., 1981) is extended so that information on the volume change on micellization may be derived from changes in slope and slope ratio of these plots. For a 3-component system we may write:

$$U^{-2} = \rho\beta \quad (1)$$

$$V = n_0V_0^0 + n_1V_1^0 + n_MV_M^0 \quad (2)$$

$$\rho = \rho_0 + (\rho_1 - \rho_0)\phi_1 + (\rho_M - \rho_0)\phi_M \quad (3)$$

$$\beta = \beta_0 + (\beta_1 - \beta_0)\phi_1 + (\beta_M - \beta_0)\phi_M \quad (4)$$

where  $U$ ,  $\rho$ ,  $\beta$ ,  $V$ ,  $V^0$ ,  $n$  and  $\phi$  denote the ultrasonic velocity, density, adiabatic compressibility, volume, molar volume, mole amounts and the volume fraction, respectively. 1, M and 0 refer to the monomer, micelle and the solvent, respectively.

Combination of Eqns. 1, 3 and 4, neglecting higher-order terms in  $\phi_1$  and  $\phi_M$  gives:

$$U^{-2} = U_0^{-2}(1 - F_1\phi_1 - F_M\phi_M) \quad (5)$$

$$F_1 = 2 - \beta_1/\beta_0 - \rho_1/\rho_0 \quad (6)$$

$$F_M = 2 - \beta_M/\beta_0 - \rho_M/\rho_0 \quad (7)$$

Eqn. 5 predicts a linear variation of the inverse of the square of the velocity with volume fraction and hence with molar concentration.

By introducing the simplest description of the equilibrium in a micelle forming system:

$$mA \rightleftharpoons A_m \quad (8)$$

where  $m$  is the aggregation number, and assuming the monomer concentration to be equal to the cmc once the micelles are formed we may rewrite Eqn. 5 as:

$$\frac{U^2 - U_0^2}{U^2} = \frac{F_M V_M^0}{m} C + \left( F_1 V_1^0 - \frac{F_M V_M^0}{m} \right) \text{cmc} \quad (9)$$

for  $C > \text{cmc}$  and

$$\frac{U^2 - U_0^2}{U^2} = F_1 V_1^0 C \quad (10)$$

for  $C < \text{cmc}$ .

Eqns. 9 and 10 predict a linear variation with the overall concentration both above and below the cmc with the slopes  $s_M$  and  $s_1$ , respectively. Comparison of Eqns. 9 and 10 shows that the abscissa value at the intersection of the two lines is equal to the cmc. Furthermore the cmc value can be obtained from the slopes  $s_1$  and  $s_M$ , and the extrapolated value,  $S$ , at zero concentration

$$\text{cmc} = \frac{S}{s_1 - s_M} \quad (11)$$

It can also be shown that the ratio of the two slopes is given by:

$$s_1/s_M = F_1/[F_M(1 - a/100)] \quad (12)$$

where  $a$  is the percentage with which the molar volume for one mole of monomer in the micelle state is smaller than that in the pure monomeric state. The larger the ratio between the two slopes the larger is the volume change involved.

The values of  $F_1$  and  $F_M$  are expected to be very small. Consequently the ratio of  $F_1$  to  $F_M$  cannot be approximated to unity. However, the effect of a small variation

in the temperature, although it affects  $F_1$  and  $F_M$ , may be assumed to cancel in the ratio. For measurements carried out at two different temperatures,  $T_1$  and  $T_2$ , the following approximation can thus be introduced:

$$a_{T_2} = 100(1 - \gamma_{1,2}) + \gamma_{1,2}a_{T_1} \quad (13)$$

$$\gamma_{1,2} = \left( \frac{s_1}{s_M} \right)_{T_1} / \left( \frac{s_1}{s_M} \right)_{T_2} \quad (14)$$

It must be stressed that Eqn. 13 is a reasonable approximation only if  $\gamma_{1,2}$  is close to unity, i.e. only small temperature variations are involved. In terms of the approximation involved in Eqn. 13 we can express:

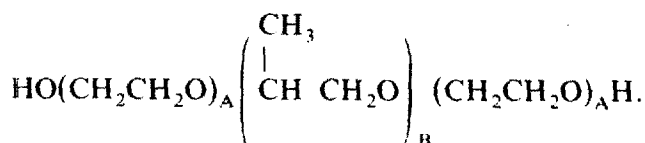
$$\frac{\Delta a}{\Delta T} = \frac{1 - \gamma_{1,2}}{T_2 - T_1} (100 - a_1) \approx \frac{1 - \gamma_{1,2}}{T_2 - T_1} 100 \quad (15)$$

Consequently the temperature dependence of the volume change involved in the micellization process can be calculated from the velocity concentration profiles at different temperatures.

## Materials and Methods

### Materials

Pluronic F127 was a gift from BASF Wyandotte and was used as received. All measurements were carried out on the same batch of this compound. F127 is an ABA block copolymer containing approximately 70% oxyethylene with a nominal molecular weight  $1.15 \times 10^4$  and general formula,



### Methods

*Ultrasonic velocity measurements* were made by the ring-around technique (Rassing, 1971) using a modified NUS-sonic solution Monitor (NUSonics). The temperature,  $T$ , of the sample was measured by means of a quartz thermometer and was constant to within  $\pm 0.1^\circ\text{C}$ . The ultrasonic velocity,  $U$ , was corrected for these small temperature fluctuations by means of a  $dU/dT$  value determined at each concentration.

*Light scattering measurements* were carried out using a Fica 42,000 photogoniometer at a wavelength of 546 nm. Solutions were clarified by ultrafiltration through  $0.22 \mu\text{m}$  Millipore filters. Temperature control was  $\pm 0.1^\circ\text{C}$ . The refractive index increments were measured at 546 nm using a differential refractometer thermostatted to  $\pm 0.1^\circ\text{C}$ .

## Results

Figs. 1 and 2 show distinct inflection points in the plots of  $U^2 - U_0^2/U^2$  against  $C$  and non-zero ordinate values, when the data at high concentrations are extrapolated to zero concentration clearly indicating the micellar nature of the association process over the temperature range 20–31°C. Cmc values calculated from Eqn. 11 and from the value at the inflection point were in good agreement and are given in Table 1. The temperature dependence of the volume change as determined from Eqn. 15 was  $-2\%/^{\circ}\text{C}$ , in the temperature range 20–31°C. At 17.1°C the plot shows no inflection and passes through the origin indicating a lack of any significant association at concentrations less than 1%.

The concentration dependence of the light-scattering intensity at a scattering angle of  $90^{\circ}$  to the incident beam,  $S_{90}$ , is shown in Figs. 3 and 4 at a series of temperatures over the range 10–40°C. Inflection points were noted at 10°C and at temperatures above 25°C. Agreement between the cmc values at 30°C from light scattering and ultrasonic velocity techniques was good (Table 1). The angular scattering envelopes of solutions at temperatures of 25°C and above were symmetrical, as shown by values of the ratio of light-scattering intensities at angles of  $45^{\circ}$  and  $135^{\circ}$ , ( $z^{45}$ ), of close to unity, indicating spheroidal micelles. Plots of  $(C - \text{cmc})/(S_{90} - S_{90\text{cmc}})$  against  $(C - \text{cmc})$  were linear and weight-average micellar weights were calculated from the intercept at  $C = \text{cmc}$  in the usual manner. Table 1 shows a

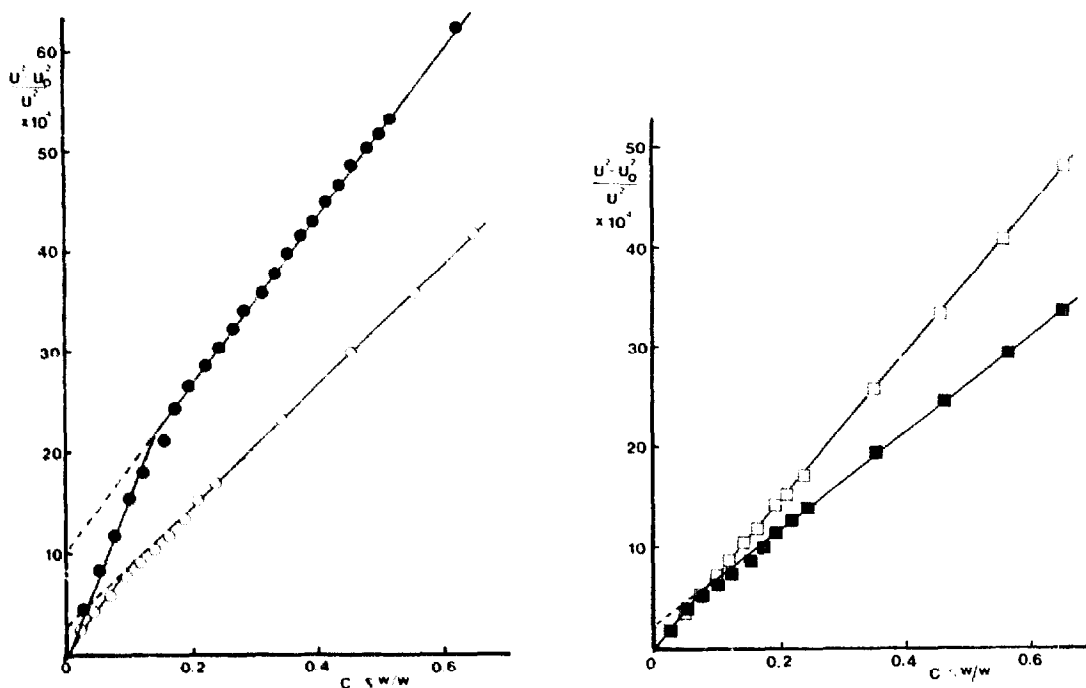


Fig. 1. Ultrasonic velocity data plotted in accordance with Eqn. 9 at: ●, 20.0°C; and ○, 25.5°C.

Fig. 2. Ultrasonic velocity data plotted in accordance with Eqn. 9 at: □, 17.1°C; and ■, 31.0°C.

TABLE 1  
MICELLAR PROPERTIES OF PLURONIC F127

Temperature (°C)	Refractive index increment (ml·g <sup>-1</sup> )	Molecular weight × 10 <sup>-4</sup>	Aggregation number <sup>a</sup>	z <sup>45</sup>	cmc (% w/w)	
					light-scatt.	ultrason. vel.
10.0	0.124	8.8	6	1.30	1.75	-
15.0	0.123	-	-	1.40	-	-
17.5	0.122	-	-	1.38	-	> 1.0
20.0	0.121	-	-	1.25	-	0.14
25.0	0.120	-	-	1.12	-	0.095 <sup>b</sup>
30.0	0.118	21.0	15	1.09	0.08	0.075 <sup>c</sup>
35.0	0.116	28.0	20	1.10	~ 0.01	-
40.0	0.114	61.8	44	1.10	~ 0.005	-

<sup>a</sup> Calculated using experimental weight-average monomer weight of  $1.4 \times 10^5$ .

<sup>b</sup> At 25.5°C.

<sup>c</sup> At 31.0°C.

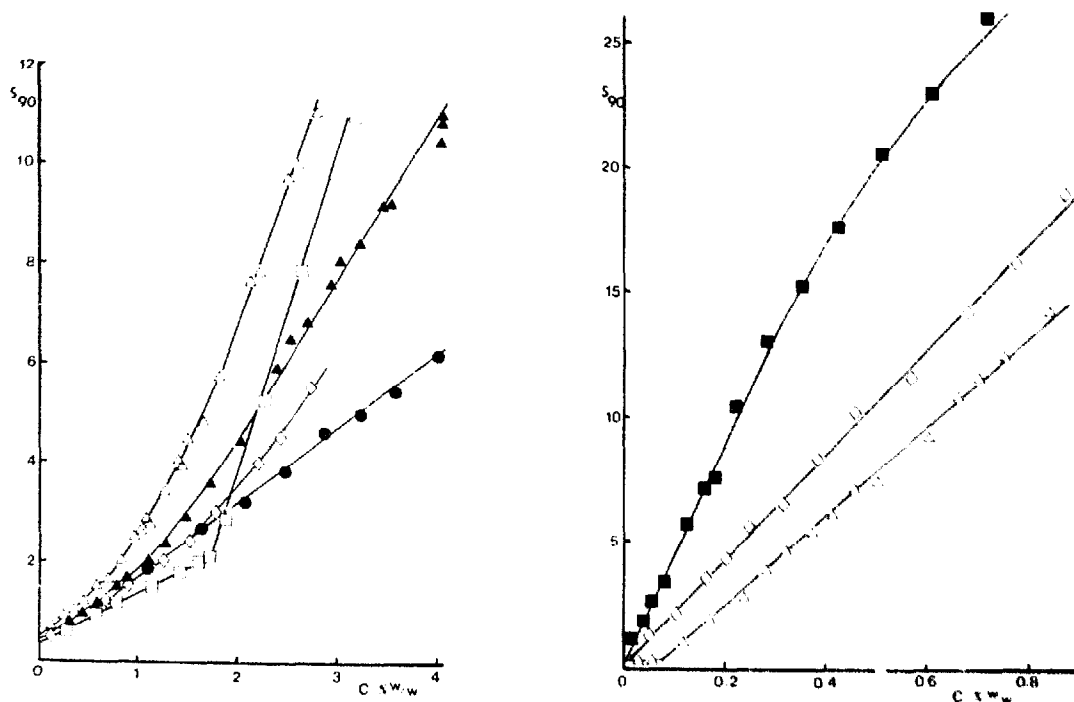


Fig. 3. Concentration dependence of the light-scattering ratio,  $S_{90}$ , at: □, 10°C; ▲, 15°C; ◇, 17.5°C; ●, 20°C; and △, 25°C.

Fig. 4. Concentration dependence of the light-scattering ratio,  $S_{90}$ , at: △, 30°C; ◇, 35°C; and ■, 40°C.

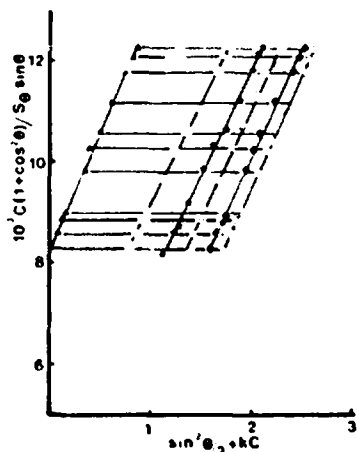


Fig. 5. Light scattering data below the cmc at 10°C plotted by the Zimm method.

pronounced increase in the size of the aggregate and a marked decrease in cmc with temperature increase above 25°C. The temperature effects were reversible;  $S_{90}$  values were independent of whether solutions were warmed or cooled to the temperature of measurement.

The intensity of light scattering from solutions over the temperature range 15–25°C was low indicating only a limited association. Inflections could not be detected in the  $S_{90}$ -C curves and the determination of micellar weight was not possible. Fig. 3 does, however, indicate a minimum association at about 20°C. As can be seen from the  $z^{45}$ -values of Table 1 there was a progressive increase in the asymmetry of the angular scattering envelope and therefore of the aggregated species as the temperature was decreased over this temperature range.

At 10°C the  $S_{90}$ -C curve exhibited a clear cmc. Asymmetric scattering envelopes were noted both above and below the cmc and the data were treated using the Zimm method of extrapolation to zero concentration and zero angle (Evans, 1972) (see Fig. 5). A weight-average monomer molecular weight of  $1.4 \times 10^4$  was determined by analysis of the data below the cmc in reasonable agreement with the nominal value ( $1.15 \times 10^4$ ) quoted by the manufacturers. A radius of gyration,  $\rho_g$ , of 41.2 nm was calculated from the slope of the zero concentration line of the Zimm plot. The average end-to-end length,  $h$ , of a linear coil as calculated from  $\rho_g^2 = \langle h^2 \rangle / 6$  was 100 nm. This value approaches that calculated for the chain-length of the F127 molecule using the dimensions of the oxyethylene and oxypropylene units proposed by Rösch (1967) and Stanley and Litt (1960) and hence suggests the presence of extended coils in solution at this temperature. A similar treatment of the data above the cmc gives an aggregation number of 6 and a radius of gyration of 32.7 nm.

## Discussion

Previous studies of the colloidal properties of polyoxyethylene-polyoxypropylene block copolymers have produced conflicting results. Dwiggin et al. (1960) and Mankowich (1954) were unable to detect association using light-scattering and ultracentrifugation techniques. McDonald and Wong (1974, 1977) also reported little or no association of Pluronic F68, F65 and L64 at 25°C but noted a marked increase in light-scattering intensity from solutions of the latter two compounds at higher temperatures. These authors were, however, unable to detect cmc values in the  $S_{90}$ -C curves and suggested that growth of aggregates to a stable size occurred over a much wider concentration range than for other non-ionic surfactants. It is clear from the ultrasonic velocity and light-scattering measurements reported here that the association of Pluronic F127 is a micellar process, although the extent of association may be limited at temperatures below 25°C. The  $U^2 - U_0^2/U^2$  vs C plots of Fig. 1 show distinct cmcs at temperatures of 20°C and 25.5°C. The failure to detect similar inflections in the light-scattering plots at these temperatures is thought to be a consequence of the limited association since it is well known from the application of the mass action law to the micellization process that the abruptness of the change in physical properties in the region of the cmc is a function of the micellar equilibrium constant and the aggregate size.

The reversible, thermal gelation of solutions of this block copolymer of high concentration is clearly explicable in terms of the very marked, reversible, temperature dependence of the micellar size which is evident in the more dilute solutions studied in this investigation as the temperature is increased above 25°C. Similar micellar enlargement has been reported (Balmbra et al., 1962; Elworthy and Florence, 1965; Atwood, 1968) in solutions of many polyoxyethylated non-ionic surfactants and indeed in some non-ionic systems such changes are noted only above a threshold temperature such as is noted here.

The changes in slope of the plots of  $U^2 - U_0^2/U^2$  against C at the cmc are very small. At 20°C the ratio of the two slopes is 2 whilst that for a typical micellization process, for example that of sodium octylsulphate, is 25. Consequently the change of molar volume of the F127 monomer when incorporated in a micelle must be relatively small and as seen from the  $\Delta a/\Delta T$  value, decreases with temperature increase. Inflections in surface tension-log concentration graphs for other polyoxamers (Prasad et al., 1979) at low solution concentration have been interpreted as implying the formation of so-called 'monomolecular micelles' in which the polyoxyethylene chains are coiled around the central hydrophobic polypropylene chain so protecting it from the aqueous environment. The high end-to-end chain-length calculated from the light-scattering data below the cmc at 10°C precludes the presence of any such structures in significant concentrations at this temperature. The difference in the radius of gyration of free monomers and aggregates is not appreciable; the aggregate is an elongated structure such as might be formed by the loose intertwining of the extended monomer coils. The decrease in  $z^{45}$  over the temperature range 10-25°C implies an increasing symmetry of the aggregates. In this respect it is of interest to note that the aggregates at 25°C are more symmetrical than those at 10°C even though they are probably of similar size.



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