International Journal of Pharmaceutics, 22 (1984) 207–218
Elsevier

IJP 00754

Thermodynamic studies on the gel–sol transition of some pluronic polyols

Madhu Vadnere *, Gordon Amidon **, Siegfried Lindenbaum and John L. Haslam

Department of Pharmaceutical Chemistry, The University of Kansas and INTER$_x$ Research Corporation, Lawrence, KS 66044 (U.S.A.)

(Received October 19th, 1983)
(Modified version received and accepted August 1st, 1984)

Summary

Studies have been carried out on a number of pluronic polyols with the aim of determining factors which influence the transition temperature of the hydrogels. The gel–sol transition temperatures, T_m, were measured for aqueous solutions of the polyols with and without additives such as sodium chloride, potassium chloride, urea, ethanol, sodium sulfate and sodium dodecylsulfate. A linear relationship was found between the logarithm of the pluronic polyol concentration and the reciprocal of the gel–sol transition temperature. Although no linear relationship was observed between log M_w (molecular weight) and the reciprocal of the gel–sol transition temperature for all polymers, such a relationship does seem to exist among the polymers having the same ratio of poly(oxypropylene) to poly(oxyethylene) units per mole of polymer, (P/E ratio). All of the pluronic polyols studied showed endothermic enthalpy change for the sol–gel process. These results were substantiated with data from calorimetric studies. The driving force for thermal gelation is a result of the large entropic change. Neither ΔH°_{gel} (for sol–gel) nor ΔS°_{gel} seem to correlate with the molecular weight of the polymer, per se; however, the number of poly(oxypropylene) units per mole of polymer plays a major role in the gelation process. The presence of sodium chloride, potassium chloride and sodium sulfate decreased the transition temperature whereas the opposite effect was observed with urea, alcohol and sodium dodecylsulfate. The enthalpy of gel formation was not

---

* Present address: Abbott Laboratories, North Chicago, IL 60064, U.S.A.

** Present address: College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109, U.S.A.

Correspondence: J.L. Haslam, INTER$_x$ Research Corporation, a subsidiary of Merck & Co., 2201 W 21st Street, Lawrence, KS 66044, U.S.A.

significantly changed by the added substances suggesting that entropy plays the major role in the gelation process.

Introduction

Pluronic polyols[1] represent a class of block copolymers, consisting of poly(oxyethylene) and poly(oxypropylene) units, with the general formula poly(oxyethylene)$_x$–poly(oxypropylene)$_y$–poly(oxyethylene)$_x$, some of which in aqueous solution at appropriate concentrations undergo thermal gelation. Variation in the number of poly(oxypropylene) and poly(oxyethylene) units and their ratio per mole of polymer provide a wide range of polyols with different physical and chemical properties (Lundsted and Schmolka, 1972a). More than a dozen areas of application have been listed for pluronic polyols (Lundsted and Schmolka, 1972b) including agricultural formulations, cosmetics, paint, paper, petroleum recovery, water treatment and formulated detergents. Because of their non-toxic nature (BASF, OS-3012 (765)), they have been investigated for pharmaceutical applications. Pluronic polymer gels have shown promising results in the area of controlled or improved drug delivery systems (Chen-Chow and Frank, 1981; Miller and Donovan, 1982). In order to develop such controlled delivery systems, it is necessary to characterize the gelation process and the effects of additives on gel formation.

Although the normal gelation process has been studied extensively (Ablett et al., 1978; Eldridge and Ferry, 1954; Marshall and Petrie, 1980; Tar and Wolfram, 1975; Tar et al., 1977), the physical-chemical characterization of the reverse or thermal gelation process has not been investigated.

Eldridge and Ferry (1954) originally reported the dependence of gel–sol transition temperature on the concentration of polymer and derived a relationship ($\ln c = \Delta H^\circ / RT_{gel \to sol} + \text{constant}$) which gives an estimate of heat of gelation, ΔH°_{gel}. This relationship has been successfully used by other investigators (Tar and Wolfram, 1975; Tar et al., 1977) to characterize the gelation process. In the present investigation we have made use of this relationship in addition to calorimetric studies.

Initial investigations indicated a positive enthalpy change for the sol–gel process. At the transition temperature T_m, an equilibrium, sol $\rightleftarrows$ gel, or phase transition exists such that

$$\Delta G^\circ = 0 \tag{1}$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{2}$$

If ΔH°_{gel} for formation of the gel is positive, then from Eqns. 1 and 2, ΔS°_{gel} must also be positive.

---

[1] BASF, Wyandotte Corp.

There thus appears to be an apparent anomaly since the formation of a gel, which is a three-dimensional network more rigid than solution and infinite in extent, would be expected to require a negative entropy change in order to produce a more "ordered" system.

A model is proposed to explain the apparent behavior of such systems.

Materials and Methods

Materials

Pluronic F-127, F-108, F-98, F-88, F-68, F-87, P-84, P-85 and P-105 (BASF Wyandotte); urea (Sigma), sodium dodecylsulfate (Kodak) were used as received. Potassium chloride (Mallinckrodt), sodium chloride and sodium sulfate anhydrous (Sigma) were dried under vacuum at 100°C for 8 h before use. Double-deionized water was used for the preparation of all solutions.

Preparation of pluronic solutions

Pluronic solutions were prepared by weighing appropriate amounts of polymer and water in 10 ml vials. The samples were refrigerated to increase the rate of dissolution. Clear solutions were obtained within 48 h in most of the cases except for very high concentrations of F-127, F-108, F-98 and P-105 which required a longer time to dissolve.

In studying the effect of additives on the transition temperature, with the exception of ethanol, appropriate amounts of additive and 30% w/w pluronic F-88 solutions were weighed. The concentration of additive was expressed as moles of additive per kg of F-88 solution. In the case of ethanol, solutions were prepared on a volumetric basis and the concentration was expressed as ml of ethanol/ml of F-88 solution.

The effect of additives on the heat of gelation was studied by preparing various concentrations of pluronic F-88 solution at a fixed concentration of additive.

Determination of gelation temperature

Glass bulbs of one ml size which are used in the TRONAC calorimeter (see section 'Calorimetric heats of gelation') were also used in the determination of gelation temperature. These glass bulbs are extremely thin which ensures negligible temperature lag between the surrounding temperature and the temperature of the contents inside the bulb. The bulb has 3.5 cm long neck with 2 mm inside diameter. About 0.25 g of polymer solution was transferred to the glass bulb using a syringe, in a cold room (temp. ≃ 4°C). Care was taken to avoid any contact of the solution with the inside of the neck. The neck was sealed using a microflame torch. The bulb was inverted and placed into an ice-cold water bath for a few minutes and then into a hot water bath in order to form an immobile gel. The neck of the bulb was attached to a glass rod and then placed into a jacketed beaker with a stir bar. To begin with, the temperature in the jacketed beaker was maintained at a higher value than T_m. The bath temperature was then reduced at a rate of about 6°C/h. The temperature at which the gel starts melting was taken as the transition temperature. In all the cases the transition was reproducible to within 0.1 °C. The gel was completely melted within 0.2–0.3 °C range. The procedure can be repeated on the same sample and the same transition temperature is observed which demonstrates the reversibility of the process.

Calorimetric heats of gelation

For these studies a TRONAC Model 450 Solution Calorimeter was used. Heats of solution of gel and sol forms were measured just above and below the transition temperature. The experiment essentially consisted of breaking a glass bulb containing about 0.200 g of aqueous polymer sample into 40 ml of water contained in a Dewar flask equilibrated at a temperature just below and just above the transition temperature. The procedure used with this calorimeter is described by Eatough et al. (1974). The calorimetric system was tested periodically by measuring the heat of protonation of tris(hydroxymethyl)aminomethane, with HCl. The value of ΔH found for this reaction at 25°C was -11.33 ± 0.04 kcal/mol which agrees well with the value of Hill et al. (1969) of -11.35 kcal/mol.

NMR studies

The percent of poly(oxypropylene) and poly(oxyethylene) units per mole of polymer were estimated from the ^{1}H NMR spectrum of the polyol in deuterated chloroform using a Perkin Elmer R-32, 90 MHz instrument. The following peaks are seen in the spectrum:

$\delta_1 = 1.15$ (d, 3H, methyl)

$\delta_2 = 3.3\text{-}3.7$ (m, 7H, methylenes)

Ratio of oxypropylene to oxyethylene units was obtained from the area under the nmr peaks as follows:

$$\text{ratio, P/E} = (\text{area } \delta_1/3)/(\text{area } (\delta_2 - \delta_1)/4)$$

Results and Discussion

The gel–sol transition temperature was measured as a function of polymer concentration for nine pluronic polyols. The concentration range was adjusted such that the transition temperatures were between 5 and 50°C. Fig. 1 shows a plot of the logarithm of polymer concentration vs $1/T$ for some of the polymers studied. All polymers show a linear relationship between log C versus $1/T$ in the concentration range of these studies with the exception of F-87. Slopes of these plots gave estimates of ΔH°_{gel} according to the following relationship (Eldridge and Ferry, 1954).

$$\ln C = \frac{\Delta H^\circ_{gel}}{RT_{gel \rightarrow sol}} + \text{constant}$$

Table 1 lists the ΔH°_{gel} values for the polymers studied. In all cases, a positive enthalpy change between 5 and 10 kcal/mole of polymer was observed. Unlike gelation of gelatin where the large enthalpy change (−67 kcal/mole) favors the gelation process (Eldridge and Ferry, 1954), the enthalpy change makes an unfavorable contribution to gelation of pluronic polyols. Calorimetric experiments were run

TABLE 1

ENTHALPY OF GELATION OBTAINED FROM GEL-SOL TRANSITION TEMPERATURE STUDIES

Pluronic polyol	Molecular weight *	r [a]	ΔH°_{gel} (kcal/mol)
F 108	14,000	0.9993	8.0
F 98	13,000	0.9982	8.1
F 127	12,500	0.9994	9.5
F 88	10,800	0.9971	6.8
F 68	8,350	0.9993	5.4
F 87	7,700	–	–
P 105	6,500	0.9994	8.6
P 85	4,600	0.9954	6.5
P 84	4,200	0.9968	6.2

* Source: BASF Wyandotte Corp., technical data, 05-796.

[a] Correlation Coefficient

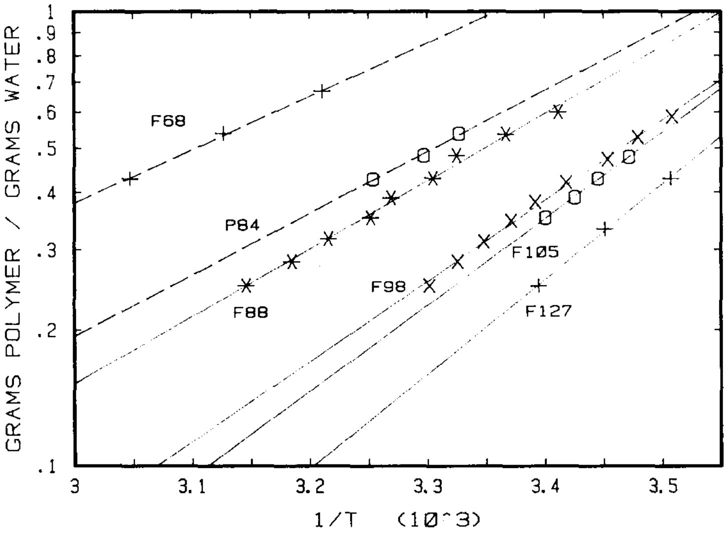

Fig. 1. Semilog plot of the concentration of various pluronic polyols vs the reciprocal of the gel to sol transition temperature.

to confirm the positive enthalpy change for the sol to gel transition.

If T_m is the transition temperature, then at a temperature of $T_m + \Delta T$ the gel form is stable and at a temperature of $T_m - \Delta T$ the solution will form. The total heat change, in going from a gel to dilute solution at $T_m + \Delta T$, may be written as follows:

$$\Delta H_{\mathrm{total}}^{(T_m+\Delta T)} = \int_{(T_m+\Delta T)}^{T_m} C_p^{\mathrm{gel}} dt + \Delta H^{\circ}_{\mathrm{gel-sol}} + \int_{T_m}^{(T_m+\Delta T)} C_p^{\mathrm{sol}} dt + \Delta H_{\mathrm{dil}}^{(T_m+\Delta T)} \qquad (3)$$

If $C_p^{\mathrm{gel}} = C_p^{\mathrm{sol}}$, then Eqn. 3 reduces to:

$$\Delta H_{\mathrm{total}}^{(T_m+\Delta T)} = \Delta H^{\circ}_{\mathrm{gel-sol}} + \Delta H_{\mathrm{dil}}^{(T_m+\Delta T)} \qquad (4)$$

The total heat change at $(T_m - \Delta T)$ will only involve a heat of dilution;

$$\Delta H_{\mathrm{total}}^{(T_m-\Delta T)} = \Delta H_{\mathrm{dil}}^{(T_m-\Delta T)} \qquad (5)$$

Further, if it is assumed that $\Delta H_{\mathrm{dil}}^{(T_m-\Delta T)} \simeq \Delta H_{\mathrm{dil}}^{(T_m+\Delta T)}$, for given dilution, then from Eqns. 4 and 5

$$\Delta H_{\mathrm{sol-gel}} = \Delta H_{\mathrm{gelation}} = \Delta H_{\mathrm{total}}^{(T_m-\Delta T)} - \Delta H_{\mathrm{total}}^{(T_m+\Delta T)} \qquad (6)$$

Thus, the difference of heats of solution at a temperature just below and just above T_m would give an estimate of ΔH of transition.

Table 2 summarizes the results of a calorimetric study on two gels: F-98 and F-108. In both cases, the direction of the enthalpy change is the same as that observed from the concentration–temperature relationship. The magnitude of the ΔH is also comparable with those in Table 1 considering the assumptions made in the above treatment.

It is apparent from Table 1 that there is no correlation between the molecular

TABLE 2

ENTHALPY OF GELATION OBTAINED FROM CALORIMETRIC STUDIES

Sample	Transition temp. (°C)	Bath temp. °C)	Process involved	ΔH total (kcal/mol)	Approximate ΔH/sol-gel (kcal/mol)
23.8% w/w	25.55	25.70	Gel—dilute solution	−100.3 ± 0.8	7.9 ± 1.3
F 98		23.50	Sol—dilute solution	−92.4 ± 1.0	
30.0% w/w	19.8	19.90	Gel—dilute solution	−127.6 ± 2.0	6.2 ± 2.2
F 108		17.50	Sol—dilute solution	−121.4 ± 0.5	

weight of the polymer and ΔH°_{gel}. Other attempts to relate the physical properties of pluronic polyols to their molecular weight have also been unsuccessful (Lundsted and Schmolka, 1972a). Here, we propose a hypothesis that the thermodynamic functions (ΔH°_{gel} and ΔS°_{gel}) associated with the sol $\rightleftarrows$ gel transition are a linear combination of the number of poly(oxypropylene) (P) and poly(oxyethylene) (E) units per mole of polymer. Regression analysis gives the following expression for heat of gelation,

$$\Delta H^{\circ}_{gel} = a \cdot P + b \cdot E \qquad (7)$$

where a = enthalpy contribution/poly(oxypropylene) unit; P = number of poly(oxypropylene) units/mole of polymer; b = enthalpy contribution/poly(oxyethylene) unit; E = number of poly(oxyethylene) units/mole of polymer.

NMR studies were performed as described previously to estimate P and E. Results of these experiments along with the manufacturer's data are listed in Table 3. It is seen that in all the cases poly(oxypropylene) content per mole of polymer was smaller than the reported by the manufacturer.

Both sets of data, from the NMR studies and that supplied by the manufacturer, were used in the estimation of a and b from Eqn. 7. The estimated values for a and b are given in Table 4. The correlation between observed enthalpy and the enthalpy calculated from Eqn. 7 are plotted in Fig. 2.

A good correlation is obtained using Eqn. 7. A similar equation can also be written for the entropy,

$$\Delta S^{\circ}_{gel} = a' \cdot P + b' \cdot E \qquad (8)$$

TABLE 3

WEIGHT PERCENT AND NUMBER OF POLY(OXYETHYLENE) AND POLY(OXYPROPYLENE) UNITS PER MOLE OF POLYMER

Polymer	NMR studies				From manufacturer's data			
	wt.% [a]	P [b]	E [c]	P/E	wt.% [a]	P [b]	E [c]	P/E
F 108	15.6	38	268	0.14	20	48	255	0.19
F 98	16.5	37	247	0.15	20	45	236	0.19
F 127	27.2	59	207	0.29	30	65	199	0.32
F 88	18.0	34	201	0.17	20	37	196	0.19
F 68	17.4	25	157	0.16	20	29	152	0.19
F 87	27.5	37	127	0.29	30	40	123	0.33
P 105	46.1	52	80	0.65	50	56	74	0.76
P 85	45.8	36	57	0.63	50	40	52	0.77
P 84	55.8	40	42	0.95	60	43	38	1.13

[a] w/w% of poly(oxypropylene) per mole of polyol.

[b] Number of poly(oxypropylene) units per mole of polyol.

[c] Number of poly(oxyethylene) units per mole of polyol.

where a′ = entropy contribution/propylene unit; and b′ = entropy contribution/ethylene unit.

The estimated values of a′ and b′ are also given in Table 4 and a similar correlation between the observed and calculated values of ΔS°_{gel} is obtained. The number of poly(oxypropylene) units in these polymers is a dominant factor in determining the gelling temperature. The number of poly(oxypropylene) units/mole increases as one goes from F-68 through F-127. Thus, each additional poly(oxypropylene) unit contributes an increase in both ΔH°_{gel} and ΔS°_{gel} but the entropy contribution overrides the enthalpy contribution so that a decrease in gelation temperature is observed, at a given concentration of polymer, with increasing poly(oxypropylene) units. Table 5 gives the calculated values of ΔS for a 25% (w/w) solution of the polymer in water.

Fig. 3 shows the concentration of polymer required to give a gel transition temperature of 25°C plotted as a function of P/E ratio. Two trends are noted. At

TABLE 4

ESTIMATES OF ENTHALPIC AND ENTROPIC CONTRIBUTIONS PER UNIT OF POLY(OXYETHYLENE) AND POLY(OXYPROPYLENE)

Based on:	a (cal/mol)	b (cal/mol)	$a' \times 10^2$ (e.u.)	$b' \times 10^2$ (e.u.)
Manufacturer's data	141.2 ± 7.9	6.0 ± 2.2	47.1 ± 2.1	1.9 ± 0.6
NMR data	150.3 ± 4.6	9.2 ± 1.2	49.8 ± 1.7	3.0 ± 0.4

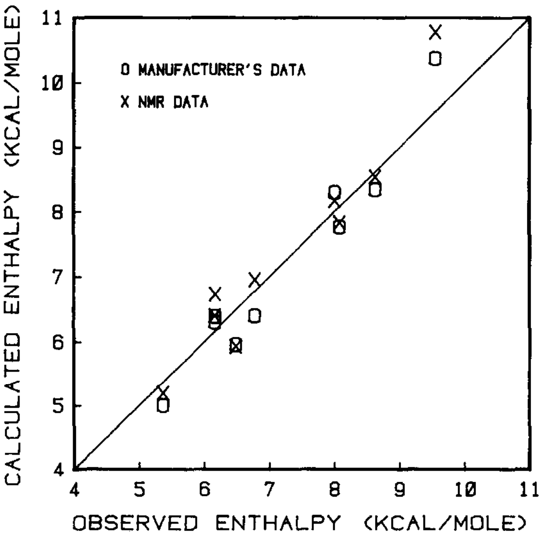

Fig. 2. Plot of the calculated enthalpy (Eqn. 7) against the observed enthalpy (Table 1). The line represents a correlation.

the fixed weight of poly(oxypropylene) units per mole of polymer (P-84, P-85, F-88) there is little difference in concentration to achieve the same transition temperature. Also, at the given ratio of P/E (F-68, F-88, F-98) the concentration required to achieve the same gelation temperature decreases with increasing poly(oxypropylene) hydrophobe. Further, in a series of polymers with similar P/E ratio, a linear relationship would then exist between log M_w and 1/T which is the case with the series F68, F88 and F98.

Effect of additives

To further investigate the property of thermal gelation, the effect of additives on gel–sol transition temperature was determined. Fig. 4 shows the effect of several additives on the gelation temperature. The effect of NaCl, KCl and Na_2SO_4 is to

TABLE 5

ENTROPY OF GELATION FOR 25% (w/w) PLURONIC POLYOLS

Pluronic polyol	$\Delta S°$ (e.u.)
F 108	26.87
F 98	27.20
F 127	32.98
F 88	21.90
F 68	15.85
F 87	–
P 105	29.23
P 85	20.84
P 84	19.62

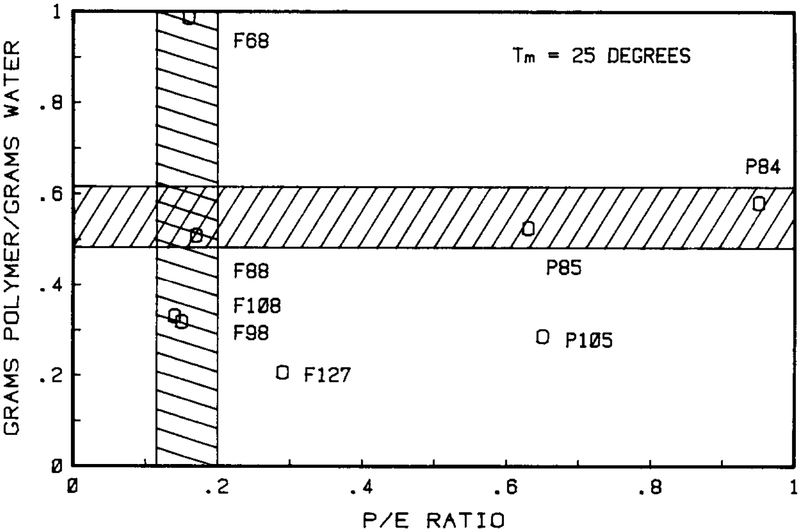

Fig. 3. The concentration of polyol to give a gel to sol transition of 25°C plotted against the ratio of poly(oxypropylene) to poly(oxyethylene). See text for explanation of the two hatched regions.

lower the transition temperature whereas urea, alcohol and sodium dodecylsulfate (SDS; not shown in Fig. 4) produce an increase. The effects of inorganic salts can be viewed in terms of reducing the water activity and as a result they increase the effective concentration of polymer in the system. As observed, an increase in polymer concentration lowers the gel transition temperature.

Urea, alcohol and SDS have the opposite effect on the transition temperature. Some workers have attributed the effect of SDS to micellar solubilization (Chen Chow and Frank, 1981). Although this may be partially true in the case of SDS, this is not the case for urea and alcohol. Urea is known to be a water structure breaker (Mastroianni et al., 1972) and alcohol also reduces hydrophobic interactions (Ben-Naim, 1980). These observations suggest that the changes brought about by these additives are due to the disruption of the hydration sphere presumably around the hydrophobic portion of the molecule.

Any molecular picture to account for the observed data is speculative. The observed ΔH and ΔS values result from both solvent and solute interactions and in addition intramolecular changes in the polymer chains. However, the highly schematic model shown in Fig. 5 provides a qualitatively correct explanation of the observed data. According to this model, there exists a local higher order of water molecules around the hydrophobic unit of the polymer in solution. As gelation occurs the interaction between the hydrophobe unit of polymer molecules, squeezes out these ordered water molecules into the bulk solution of lower order. This results in an overall disorder or increased entropy which is the driving force for hydro-

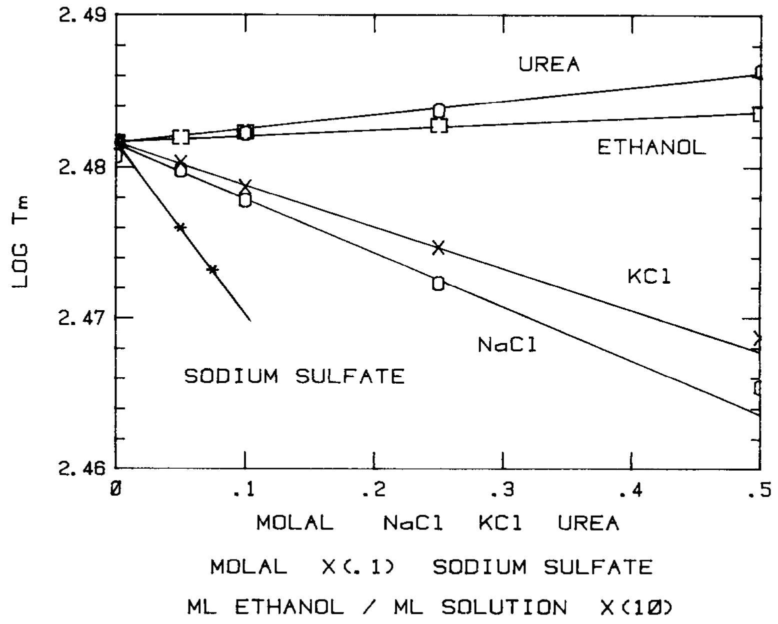

Fig. 4. A plot of the logarithm of the gelling temperature of a 30% solution of pluronic F88 as a function of various water-soluble additives.

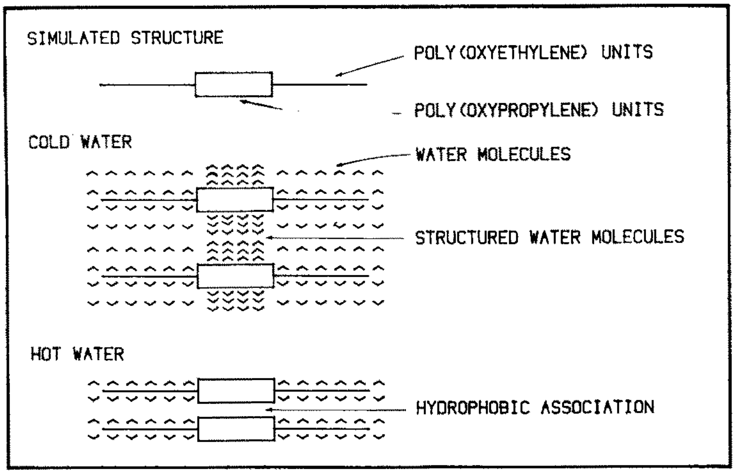

Fig. 5. Schematic representation of a typical pluronic polyol and a proposed mechanism for the gelation process:
cold water—solution of polymer in water;
hot water—gelled polymer in water

phobic association. Furthermore, hydrophobic interactions are characterized by endothermic heat changes, which is the case in the gelation of pluronic polyol solutions. The model is consistent with the effect of urea and alcohol. Urea and alcohol are expected to perturb the hydration sphere, thus lowering the local higher order of water molecules and consequently reducing the driving force for hydrophobic interaction. It is interesting to note that the reverse pluronic polyols poly(oxypropylene)–poly(oxyethylene)–poly(oxypropylene) do not form gels but reach a cloud point as the temperature is raised. This indicates that there is a very sensitive balance between polymer association and hydration in order to form a gel.

Thermodynamic data, in and of themselves, cannot give structural information so the molecular picture is speculative, and in a recent paper (Rassing and Attwood, 1983), the thermal gelation of these polymers was attributed to a reversible increase in the size of the aggregate. The driving force for such an association could be ascribed to the same type of hydrophobic association described here.

References

Ablett, S., Lillford, P.J., Baghdadi, M.A. and Derbyshire, W., Nuclear magnetic resonance investigations of polysaccharide films, sols and gels. J. Colloid Interface Sci., 67 (1978) 355–377.

BASF Wyandotte Corp., Pluronic Polyols, Toxicity and Irritation Data, Publication No. 05-3012 (765), Wyandotte, MI.

BASF Wyandotte Corp., Technical Data on Pluronic Polyols, Publication No. 05-796 Wyandotte, MI.

Ben-Naim, A., Hydrophobic Interactions, Plenum Press, New York, 1980.

Chen-Chow, P. and Frank, S.G., In vitro release of lidocaine from pluronic F-127 gels. Int. J. Pharm., 8 (1981) 89–99.

Eatough, D.J., Christensen, J.J. and Izatt, R.M., Experiments in Thermalmetric Calorimetry, B.Y.U. Press, Provo, UT, 1974.

Eldridge, J.E. and Ferry, J.D., Studies of the cross-linking process in gelation gels. III. Dependence of melting point on concentration and molecular weight. J. Phys. Chem., 58 (1954) 975–992.

Hill, J.O., Ojelund, G. and Wadsö, I., Thermochemical results for Tris(Tris(hydroxymethyl)aminomethane) as a test substance in solution calorimetry. J. Chem. Thermodynam., 1, (1969), 111.

Lundsted, L.G. and Schmolka, I.R., The synthesis and properties of block copolymer polyol surfactants. In Ceresa (Ed.), Block and Graft Polymerization, Vol. 2, John Wiley, London, 1972, pp. 1–103.

Lundsted, L.G. and Schmolka, I.R., The application of block copolymer surfactants. In Ceresa (Ed.), Block and Graft Polymerization, Vol. 2, John Wiley, London, 1972, pp. 113–254.

Marshall, A.S. and Petrie, S.E.B., Thermal transition in gelatin and aqueous gelatin solutions. J. Photographic Sci., 28 (1980) 128–134.

Mastroianni, M.J., Pikal, M.N. and Lindenbaum, S., Effect of dimethylsulfoxide, urea, guanidine hydrochloride and sodium chloride on hydrophobic interactions. Heats of dilution of tetrabutylammonium bromide and lithium bromide in mixed aqueous solvent systems. J. Phys. Chem., 76 (1972) 3050–3057.

Miller, S.C. and Donovan, M.D., Effect of poloxomer 407 gel on the miotic activity of pilocarpine nitrate in rabbits. Int. J. Pharm., 12 (1982) 147–152.

Rassing, J. and Attwood, D., Ultrasonic velocity and light-scattering studies on polyoxyethylene–polyoxypropylene copolymer pluronic F-127 in aqueous solution. Int. J. Pharm., 13 (1983) 47–55.

Tar, I. and Wolfram, E., The effect of co-solved substances on the gel–sol transition of gelatin. In Wolfram., E. (Ed.) Proceedings of the International Conference on Colloid and Surface Science, Vol. 1, 1975, pp. 445–461.

Tar, I., Fodor Z. and Wolfram, E., Studies on the gel–sol transition and some gel characteristics of photographic gelatine. Br. Polymer J., 9 (1977) 299–301.