

## Loss of gelation ability of Pluronic® F127 in the presence of some salts

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Received 18 June 1996; revised 16 September 1996; accepted 16 September 1996

### Abstract

In this investigation, we show that certain salts with multivalent anions, at characteristic concentrations, prevent Pluronic® F127 solutions from forming gels. This was done by measuring the gel formation ( $T_1$ ), gel melting ( $T_2$ ) and cloud point ( $T_{cp}$ ) transitions of 20% Pluronic® F127 gels in the presence of various such salts. All the salts studied lower all three transition temperatures. The degree of lowering is proportional to salt concentration and can be ascribed to salting-out effects. Both the cation and anion appear to influence  $T_1$ , while  $T_2$  and  $T_{cp}$  are predominantly influenced by the salt anion.  $T_1$  is lowered because salts decrease the critical micelle concentration (cmc) of F127. The effect on  $T_2$  and  $T_{cp}$  parallels the precipitation of poly(ethylene oxide) from aqueous solution in the presence of salts and follows the Hofmeister series. Multivalent anions reduce  $T_2$  to a much greater extent than  $T_1$ , and this results in a loss of gel formation above a certain 'no-gel' salt concentration. Copyright © 1996 Elsevier Science B.V.

**Keywords:** Pluronic®; Gels; Cloud point; Triblock copolymer

### 1. Introduction

Poloxamers or Pluronics® (BASF, Parsippany, NJ) are poly(ethylene oxide)–(polypropylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO) triblock copolymers which form micelles at low concentrations and clear, thermoreversible gels at high concentrations. These gels have received increasing attention over the years as drug delivery

systems for topical, transdermal, ophthalmic and implantable application (Miller and Donovan, 1982; Chi and Jun, 1990; Pec et al., 1992; Miyazaki et al., 1995; Suh and Jun, 1996). Pluronic® F127 (F127), which has a nominal molecular weight of 12 500 and a PEO/PPO ratio of 2:1 by weight, has been the most widely used of these block copolymers in pharmaceutical systems.

It has long been known that aqueous solutions of F127 above a concentration of about 20%

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(w/w) are liquid when refrigerated, but gel upon warming (Schmolka, 1972). This gel formation process has been extensively studied over the years (Rassing et al., 1984; Vadnere et al., 1984; Wanka et al., 1990; Brown et al., 1991; Linse, 1993). These studies show that gel formation occurs due to the progressive dehydration of the polymer micelles as temperature increases, leading to increased chain entanglement. The physicochemical properties of F127 gels have been studied (Gilbert et al., 1986, 1987; Wanka et al., 1990; Brown et al., 1991; Pec et al., 1992) and the influence of additives on the gel formation temperature ( $T_1$ ) and gel viscosity of some systems has been reported (Gilbert et al., 1987; Malmsten and Lindman, 1992). These studies show that inorganic salts in these gels affect  $T_1$  significantly.

If the temperature of the gel is increased above  $T_1$ , two additional transitions are observed, first a gel melting ( $T_2$ ) and then a cloud point ( $T_{cp}$ ; Malmsten and Lindman, 1992). Thus, the system is a gel between  $T_1$  and  $T_2$ , and liquid at temperatures outside this range. Very little information is available on the effect of salts on  $T_2$  and  $T_{cp}$  of F127 gels. Malmsten and Lindman studied the effect of two salts (NaCl and NaSCN) on  $T_1$ ,  $T_2$  and  $T_{cp}$ , using 30% F127 gels. Their results showed that gels formed in the presence of both salts, but all the transition temperatures changed. NaCl decreased  $T_1$ ,  $T_2$  and  $T_{cp}$  to about the same extent, while NaSCN increased  $T_1$ ,  $T_2$  and  $T_{cp}$  similarly. The net effect was that the gel region in the presence of NaCl was moved to lower temperatures, while that in the presence of NaSCN was moved to higher temperatures. This is consistent with the salting-out and salting-in properties of NaCl and NaSCN, respectively.

Since almost all pharmaceutical F127 gels are formulated with buffer salts (Gilbert et al., 1986; Johnston et al., 1992; Allen, 1993; Miyazaki et al., 1995; Suh and Jun, 1996), and may contain the salt form of a drug, we felt it was important to further investigate the effect of common inorganic salts on these transition temperatures. In particular, we were interested in studying salts that have been shown to have large effects on

the cloud points of non-ionic surfactants, to see whether gel transition temperatures are similarly affected. In addition, inorganic salts are often used for altering the solvent properties of water, and thus influencing the aggregation properties of surfactants. We can potentially use appropriate salts to tailor the temperatures at which these transitions in F127 gels occur, to design unique thermoresponsive drug delivery systems. The alteration of these transition temperatures may also influence the diffusion of the drug in the gel and, hence, release rates.

We report here the effect of NaCl,  $\text{Na}_2\text{SO}_4$ ,  $\text{Na}_3\text{PO}_4$ ,  $\text{CaCl}_2$ ,  $\text{MgSO}_4$  and  $\text{Al}_2(\text{SO}_4)_3$  on the three transitions of 20% F127 gels. We chose to use 20% F127 gels instead of the 30% F127 systems used by Malmsten and Lindman (1992), so that  $T_2$  and  $T_{cp}$  temperatures are in a pharmaceutically and physiologically relevant temperature range. Our results show patterns of behavior different from that seen with NaCl and NaSCN, in that some of these salts affect  $T_1$  and  $T_2$  to different degrees. In some of these systems, F127 loses its ability to form gels because these salts affect  $T_2$  more dramatically than  $T_1$ . Although the effect of salts on  $T_1$  has been well documented in the literature, we included it in our experiments and in this report for completeness. Similarly, we include our results with NaCl, since we have used 20% rather than 30% F127 systems. As will be seen from our results, the melting and cloud point transitions are important and need to be considered in formulating and understanding the behavior of Pluronic® gels.

## 2. Materials and methods

### 2.1. Materials

Pluronic® F127 (gift from BASF), NaCl,  $\text{Na}_2\text{SO}_4$ ,  $\text{Na}_3\text{PO}_4$ ,  $\text{CaCl}_2$ ,  $\text{MgSO}_4$  and  $\text{Al}_2(\text{SO}_4)_3$  (Aldrich Chemical Company, Milwaukee, WI) were used as received. Four different batches of F127 were used in our studies, and gave very similar results. Water was deionized and purified through a Millipore water purification system.

## 2.2. F127 gel preparation

Gels were prepared on a weight/weight basis by the cold method (Schmolka, 1972): F127 and any additives were weighed out and mixed with an appropriate quantity of water. The mixture was placed in a refrigerator until a clear, homogenous liquid formed. For cases where the gel formation temperature was very low, the mixtures were placed in a freezer for just enough time to form clear liquids. All the studies with salts used 20% (w/w) F127.

## 2.3. Determination of $T_1$ and $T_2$

The solution was then heated slowly (about 1°C/min) in a covered container with gentle stirring by a magnetic stirrer until a gel formed. Gel formation was taken as the point where there was no flow when the container was overturned. The temperature was noted and designated as  $T_1$ , or the gel formation temperature. The gel was then placed in an oven at a temperature set to be about 8–10°C above the expected gel melting temperature. The gel eventually liquefied and formed a clear, viscous liquid. At this point, the container was removed from the oven and allowed to cool under ambient conditions with gentle stirring. The temperature at which the gel reformed, as indicated by a lack of flow on overturning the container, was noted and designated as  $T_2$ , or the gel melting temperature. Although very simple, this technique of determining gel formation temperatures is commonly used for Pluronic® gels (Tan-odekaew et al., 1993) and gives reproducible results. We duplicated some experiments reported in the literature to validate our technique; these are discussed in Section 3. Although the  $T_1$  and  $T_2$  transitions are reversible, it was easier and more reproducible to measure the transition temperature when going from the liquid to gel state in both cases. We believe that this is due to the more even heating/cooling of the system when it is in the liquid state because stirring is possible.

## 2.4. Determination of $T_{cp}$

In the presence of many of the salts, the system phase separated in the oven to give a milky gel and a clear liquid. When removed from the oven and cooled with stirring, the gel first melted to give a cloudy liquid and the system then immediately cleared to give a clear, isotropic liquid. This temperature was the cloud point of the system and is designated as  $T_{cp}$ . Upon further cooling, the clear liquid formed a gel at  $T_2$ . Both temperatures were noted.

The  $T_1$ ,  $T_2$  and  $T_{cp}$  transitions occur sharply over a 1–2°C range. We performed three replicates of each measurement; our results were reproducible within  $\pm 1^\circ\text{C}$ . Stirring speed and heating/cooling rates did not significantly affect the transition temperatures.

## 3. Results and discussion

### 3.1. Effect of F127 concentration on $T_1$ and $T_2$

Although previous workers have reported on the effect of F127 concentration on gel forma-

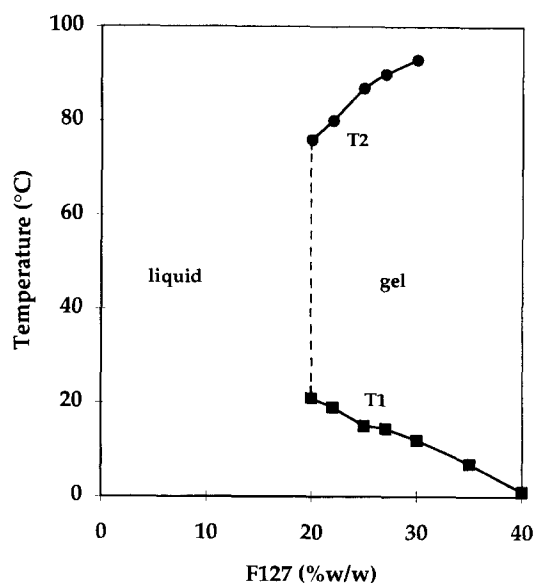


Fig. 1. Effect of F127 concentration on  $T_1$  (■) and  $T_2$  (●). No gels are observed at F127 concentrations below 20% (w/w).

tion and melting, we report our results for completeness and for providing a framework for the results with salts. Fig. 1 shows our  $T_1$  and  $T_2$  values obtained with F127 gels of various concentrations. They agree well with previous literature reports. As observed in some earlier studies (Vadnere et al., 1984; Gilbert et al., 1986, 1987), systems containing less than 20% (w/w) F127 did not form gels. For systems above 20% (w/w) F127,  $T_1$  decreased as F127 concentration increased, consistent with previous observations. An explanation of the mechanism of gel formation can be found in earlier reports (Mortensen, 1992; Linse, 1993).

As the temperature is increased above  $T_1$ , the gels liquefy at a characteristic temperature,  $T_2$ , due to the melting of the liquid crystalline gel phase (Malmsten and Lindman, 1992).  $T_2$  increases with increasing F127 concentration. At F127 concentrations above 40% (w/w), the system remained a gel in the entire temperature range 0–100°C. (The highest concentration we studied was 80% (w/w) F127). Our results are consistent with those observed previously (Malmsten and Lindman, 1992). As the weight fraction and therefore the volume fraction of F127 micelles increases as a result of an increase in F127 concentration, the micelles in the gel phase become more tightly packed; this results in an increase in  $T_2$ .

A third cloud point transition ( $T_{cp}$ ) has been reported at temperatures above  $T_2$  (Malmsten and Lindman, 1992). For F127 gels without any additives, this occurs at about 110°C and is independent of gel concentration. Our experimental temperature range went up to 100°C only, and we did not characterize this transition in the absence of salts. We did, however, observe  $T_{cp}$  in the presence of salts; these results are reported below.

### 3.2. Effect of salts on phase transition temperatures

The effect of six different salts on the transition temperatures of a 20% (w/w) F127 system is shown in Figs. 2–7. If the change in phase transition temperatures with increasing salt concentration is approximated by a straight line, the slopes

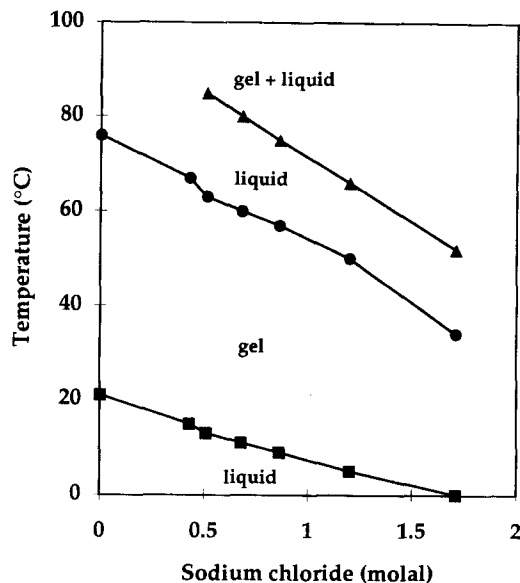


Fig. 2. Effect of NaCl on  $T_1$  (■),  $T_2$  (●) and  $T_{cp}$  (▲) of a 20% (w/w) F127 gel.

of the lines obtained are shown in Table 1. The use of this approach is merely to enable us to compare the relative effectiveness of various salts in changing the transition temperatures and is not

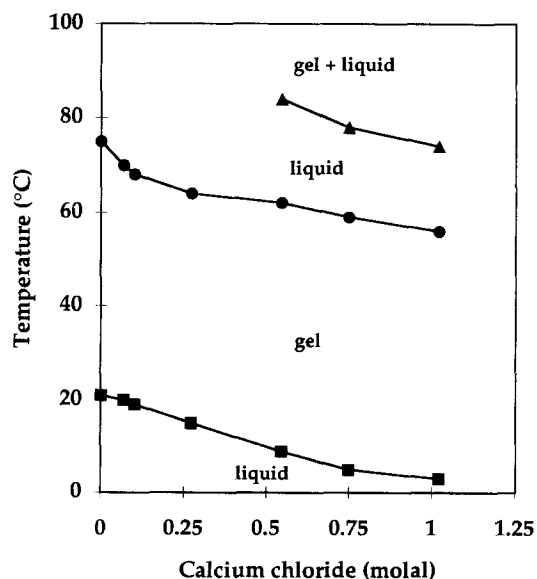


Fig. 3. Effect of CaCl<sub>2</sub> on  $T_1$  (■),  $T_2$  (●) and  $T_{cp}$  (▲) of a 20% (w/w) F127 gel.

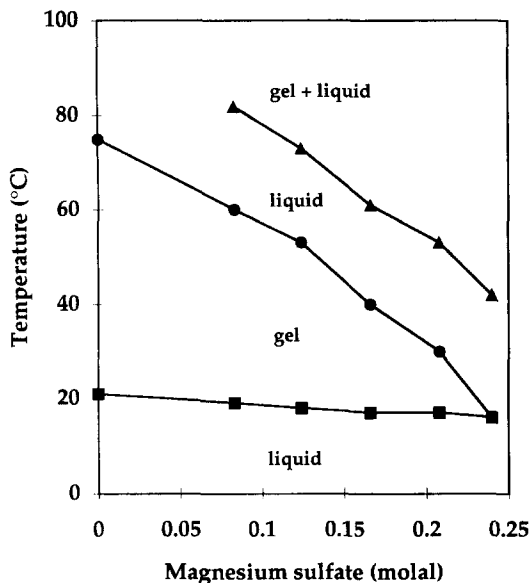


Fig. 4. Effect of MgSO<sub>4</sub> on T<sub>1</sub> (■), T<sub>2</sub> (●) and T<sub>cp</sub> (▲) of a 20% (w/w) F127 gel.

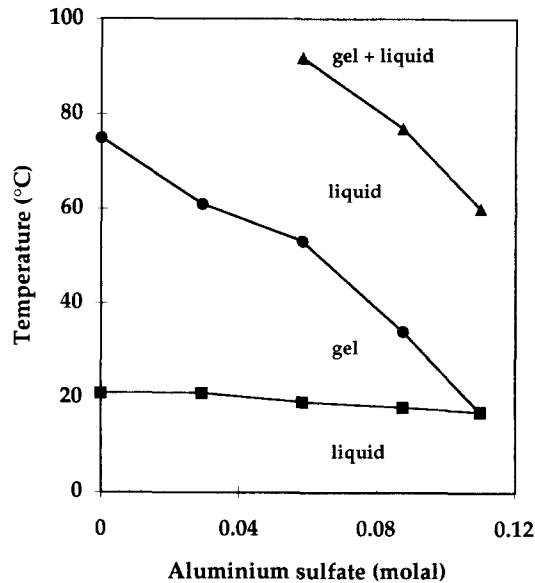


Fig. 6. Effect of Al<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> on T<sub>1</sub> (■), T<sub>2</sub> (●) and T<sub>cp</sub> (▲) of a 20% (w/w) F127 gel.

meant to imply any mechanistic relationship. The reduction in transition temperatures for F127–NaCl systems has been previously reported and was ascribed to the ability of inorganic salts to

reduce the water activity of the system, which effectively increases the aqueous polymer concentration by a salting-out effect (Vadnere et al., 1984; Malmsten and Lindman, 1992).

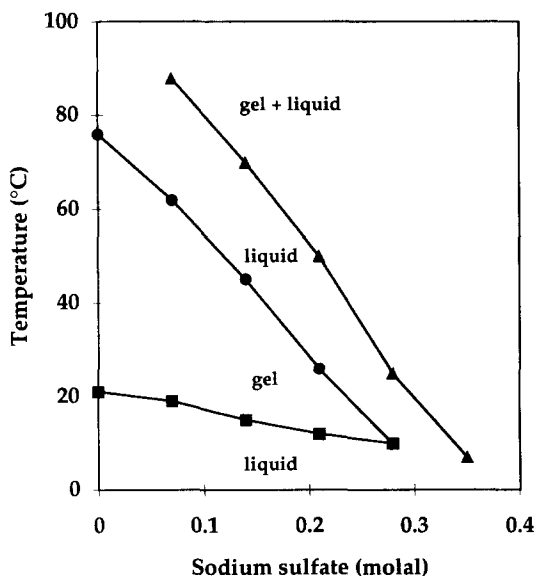


Fig. 5. Effect of Na<sub>2</sub>SO<sub>4</sub> on T<sub>1</sub> (■), T<sub>2</sub> (●) and T<sub>cp</sub> (▲) of a 20% (w/w) F127 gel.

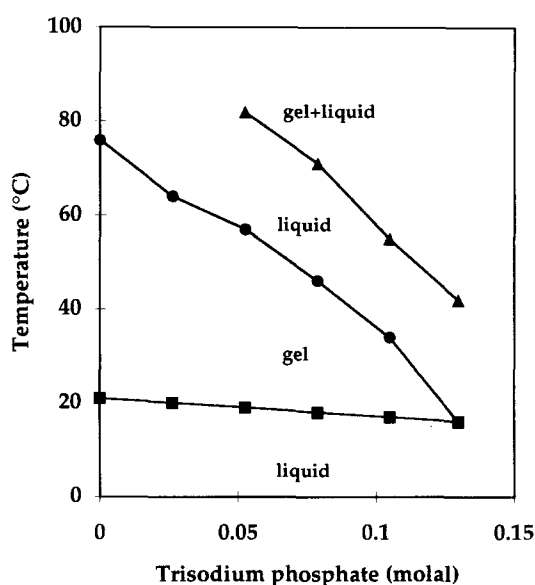


Fig. 7. Effect of Na<sub>3</sub>PO<sub>4</sub> on T<sub>1</sub> (■), T<sub>2</sub> (●) and T<sub>cp</sub> (▲) of a 20% (w/w) F127 gel.

Table 1

Effectiveness of salts at lowering  $T_1$ ,  $T_2$  and  $T_{cp}$  (effectiveness is estimated as the slope of regression lines fitted to data in Figs. 2–7)

Salt	Slope ( $-^{\circ}\text{C/molal}$ )		
	$T_1$	$T_2$	$T_{cp}$
NaCl	12	25	27
CaCl <sub>2</sub>	18	19	21
MgSO <sub>4</sub>	24	245	254
Na <sub>2</sub> SO <sub>4</sub>	37	236	289
Al <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	34	468	513
Na <sub>3</sub> PO <sub>4</sub>	31	461	516

### 3.3. Effect of salts on $T_2$ and $T_{cp}$

The effect of the salts on  $T_2$  and  $T_{cp}$  will be discussed first, since it closely parallels the phase separation of poly(oxyethylene) and PEO-containing non-ionic surfactants from aqueous solutions in the presence of these salts. Several studies have been published on this subject (Schott and Royce, 1984; Schott et al., 1984; Sjoblom et al., 1987), which show that water structure-making salts dramatically reduce the cloud points of such systems due to the enhanced dehydration of PEO chains as temperature is increased, and that the effectiveness of the salts follows the Hofmeister series. As seen in our systems, the effectiveness of the salts in lowering the transition temperature does not follow ionic strength. The anion of the salt seems to be much more effective than the cation. This is illustrated in Table 1, which shows that MgSO<sub>4</sub> and Na<sub>2</sub>SO<sub>4</sub> have about the same effect on  $T_2$  and  $T_{cp}$ , while Na<sub>3</sub>PO<sub>4</sub> is even more effective. NaCl and CaCl<sub>2</sub> have a much smaller effect on  $T_2$  and  $T_{cp}$ , with CaCl<sub>2</sub> being slightly less effective than NaCl. This is exactly the pattern seen for the salting-out of poly(oxyethylene) from aqueous solutions by salts (Bailey and Koleske, 1987).

The nature of the system above  $T_{cp}$  merits further clarification. At the cloud point ( $T_{cp}$ ), also known as the lower consolute solution temperature, the solution became visibly cloudy and separated into two phases. This is because further increases in temperature make the net interaction

between the PEO end groups attractive, resulting in phase separation into a polymer-rich and a solvent-rich phase. The  $T_{cp}$  of F127 solutions is above 100°C (which is beyond the temperature range of our studies), and was not observed in systems containing F127 and water. However, the addition of salts lowered  $T_{cp}$  sufficiently to bring it down into our experimental temperature range. Such a lowering was reported (Malmsten and Lindman, 1992) for 30% F127 gels with NaCl, but the authors did not discuss the nature of the phases above the cloud point. At the cloud point, solutions of non-ionic surfactants separate into a surfactant-rich (cloudy) phase and a surfactant-poor (clear) phase, and our systems behaved similarly. We observed that the cloudy phase, now more concentrated in F127, then gelled again. This is consistent with previous observations that  $T_2$  increases with increasing F127 concentration. The gels that formed at and above  $T_{cp}$  of the system were not transparent and clear like the gels obtained at temperatures between  $T_1$  and  $T_2$ , but were opaque two-phase systems.

### 3.4. Effect of salts on $T_1$

Table 1 reveals that the effect of the various salts on  $T_1$  shows a different pattern of behavior than their effect on  $T_2$  and  $T_{cp}$ . The quantitative differences between the salts are much smaller, and do not show the large changes seen in  $T_2$  and  $T_{cp}$  when going from monovalent to di- and trivalent anions. While the lowering of  $T_2$  and  $T_{cp}$  can be ascribed to the dehydration of the outer PEO chains of the micelles, the lowering of  $T_1$  is most probably due to a lowering of the cmc and cmt (critical micellar temperature) in the presence of salts. This facilitates closer packing of micelles and results in gel formation at lower temperatures. This implies that, at any given temperature, a gel containing these salts consists of more closely packed micelles than a similar gel without salts. This is consistent with the slower release of drugs observed in NaCl-containing F127 gels (Chen-Chow and Frank, 1981). A lowering of the cmc by salts has been shown for other non-ionic surfactants (Schott and Han, 1976).

### 3.5. Loss of gelation in the presence of salts

Salts with di- and trivalent anions lower  $T_2$  more dramatically than  $T_1$ , as seen in Table 1. In some systems, this results in the loss of gel formation at a certain critical concentration of the salt, because  $T_1$  and  $T_2$  become effectively the same at this concentration. Table 2 lists the salt and corresponding concentration above which 20% F127 will not gel. This loss of gelation ability is an important finding, because it illustrates some practical limitations to the use of F127 gels in the presence of certain cosolutes. The effect of phosphate is of particular importance, because phosphate buffer is commonly used to control pH in such gels. These results may also be relevant in understanding the behavior of Pluronic® gels in vivo, where the presence of certain anions may yield unexpected results for release rate of drugs. It is important to point out, however, that even when gelation between  $T_1$  and  $T_2$  is no longer possible, these systems gel above  $T_{cp}$  into the two-phase gel mentioned earlier.

## 4. Conclusions

We have presented a more thorough picture of the influence of water structure-making salts on the phase behavior of aqueous F127 gels.  $T_1$ ,  $T_2$  and  $T_{cp}$  are lowered by these salts. Salts with multivalent anions have a very dramatic effect on  $T_2$  and  $T_{cp}$ , leading to a loss of F127 gelation ability at certain concentrations. This behavior parallels the effect of these salts on the temperature–solubility behavior of aqueous poly(oxyethylene) solutions. The nature and degree of

the change depend in part on the ability of the salt to affect water structure, and, hence, the hydration of the PEO chain. In reality, the presence of salts probably leads to different and more complex phenomena than only the hydration or dehydration of the POE chain. One of these may be the non-specific effect of freezing point depression by an added solute, which may affect  $T_2$ . Another might be the ability of the PEO chains to form specific complexes with salts. In any event, alteration of  $T_1$ ,  $T_2$  and  $T_{cp}$ , and loss of gelation can occur at salt concentrations encountered in common buffer solutions used in gel formulations.

The study of these higher-temperature transitions of F127–water–salt systems enhances our understanding of the behavior of PEO–PPO–PEO copolymer solutions, and offers an opportunity to exploit these transitions for the design of unique thermoresponsive drug delivery systems. Since salts lower  $T_2$  and  $T_{cp}$  temperatures and bring them into physiological temperature ranges, it may be possible to exploit these transitions, besides the well-studied  $T_1$  transition, for drug delivery. In addition, the alteration of transition temperatures may alter the diffusion of drugs in the gels and, hence, influence release rates.

## References

- Allen, L.V., Ketoprofen gel. *US Pharmacist* (Nov. 1993), 98–100.
- Bailey, F.E. and Koleske, J.V., Configuration and hydrodynamic properties of the polyoxyethylene chain in solution. In Schick, M.J. (Ed.), *Nonionic Surfactants—Physical Chemistry*, Vol. 2, Surfactant Science Series, Marcel Dekker, New York, 1987, pp. 927–970.
- Brown, W., Schillen, K., Almgren, M., Hvidt, S. and Bahadur, P., Micelle and gel formation in a poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) triblock copolymer in water solution. Dynamic and static light scattering and oscillatory shear measurements. *J. Phys. Chem.*, 95 (1991) 1850–1858.
- Chen-Chow, P. and Frank, S.G., In vitro release of lidocaine from Pluronic® F127 gels. *Int. J. Pharm.*, 8 (1981) 89–99.
- Chi, S.C. and Jun, H.W., Anti-inflammatory activity of ketoprofen gel on carageenan-induced paw edema in rats. *J. Pharm. Sci.*, 79 (1990) 974–977.
- Gilbert, J.C., Hadgraft, J., Bye, A. and Brookes, L.G., Drug release from Pluronic® F127 gels. *Int. J. Pharm.*, 32 (1986) 223–228.

Table 2

Concentrations of salt above which a 20% (w/w) F127 solution loses its gel formation ability ('no-gel' concentration)

Salt	'No-gel' concentration (molal)
MgSO <sub>4</sub>	0.21
Na <sub>2</sub> SO <sub>4</sub>	0.28
Al <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	0.10
Na <sub>3</sub> PO <sub>4</sub>	0.13

- Gilbert, J.C., Washington, C., Davies, M.C. and Hadgraft, J., The behavior of Pluronic® F127 in aqueous solution studied using fluorescent probes. *Int. J. Pharm.*, 40 (1987) 93–99.
- Johnson, T.P., Punjabi, M.A. and Froelich, C.J., Sustained delivery of interleukin-2 from a poloxamer 407 gel matrix following intraperitoneal injection in mice. *Pharm. Res.* 9 (1992) 425–434.
- Linse, P., Phase behavior of poly(ethylene oxide)–poly(propylene oxide) block copolymers in aqueous solution. *J. Phys. Chem.*, 97 (1993) 13 896–13 902.
- Malmsten, M. and Lindman, B., Self-assembly in aqueous block copolymer solutions. *Macromolecules*, 25 (1992) 5440–5445.
- Miller, S.C. and Donovan, M.D., Effect of poloxamer 407 gel on the mitotic activity of pilocarpine nitrate in rabbits. *Int. J. Pharm.*, 12 (1982) 147–152.
- Miyazaki, S., Tobiyama, T., Takada, M. and Attwood, D., Percutaneous absorption of indomethacin from Pluronic® F127 gels in rats. *J. Pharm. Pharmacol.*, 47 (1995) 455–457.
- Mortensen, K., Phase behavior of poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene) triblock copolymer dissolved in water. *Europhys. Lett.*, 19 (1992) 599–604.
- Pec, E.A., Wout, Z.G. and Johnston, T.P., Biological activity of urease formulated in poloxamer 407 after intraperitoneal injection in the rat. *J. Pharm. Sci.*, 81 (1992) 626–630.
- Rassing, J., McKenna, W.P., Bandyopadhyay, S. and Eyring, E.M., Ultrasonic and  $^{13}\text{C}$  NMR studies on gel formation in aqueous solution of the ABA block polymer Pluronic® F127. *J. Mol. Liq.*, 27 (1984) 165–170.
- Schmolka, I.R., Artificial skin I. Preparation and properties of Pluronic® F127 gels for the treatment of burns. *J. Biomed. Mater. Res.*, 6 (1972) 571–582.
- Schott, H. and Han, S.K., Effect of inorganic additives on solutions of non-ionic surfactants III. Cmc's and surface properties. *J. Pharm. Sci.*, 65 (1976) 975–978.
- Schott, H. and Royce, A.E., Effect of inorganic additives on solutions of non-ionic surfactants VI: Further cloud point relations. *J. Pharm. Sci.*, 73 (1984) 793–799.
- Schott, H., Royce, A.E. and Han, S.K., Effect of inorganic additives on solutions of inorganic surfactants VII. Cloud point shift values of individual ions. *J. Colloid. Interface Sci.*, 98 (1984) 196–201.
- Sjoblom, J., Stenius, P. and Danielsson, I., Phase equilibria of nonionic surfactants and the formation of microemulsions. In Schick, M.J. (Ed.), *Nonionic Surfactants—Physical Chemistry*, Vol. 2, Surfactant Science Series, Marcel Dekker, New York, 1987, pp. 369–434.
- Suh, H. and Jun, H.W., Physicochemical and release studies of naproxen in poloxamer gels. *Int. J. Pharm.*, 129 (1996) 13–20.
- Tanodekaew, S., Deng, N.J., Smith, S., Yang, Y.W., Attwood, D. and Booth, C., Micellization and gelation of block-copoly(oxyethylene/oxybutylene) in aqueous solution. *J. Phys. Chem.*, 97 (1993) 11 847–11 852.
- Vadnere, M., Amidon, G., Lindenbaum, S. and Haslam, J., Thermodynamic studies on the gel–sol transition of some Pluronic® polyols. *Int. J. Pharm.*, 22 (1984) 207–218.
- Wanka, G., Hoffmann, H. and Ulbricht, W., The aggregation behavior of poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene)-block-copolymers in aqueous solution. *Colloid. Polym. Sci.*, 268 (1990) 101–117.