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COMMUNICATION

Gelation of Pluronic® F127-Polyethylene Glycol Mixtures: Relationship to PEG Molecular Weight

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ABSTRACT

The formation and melting of Pluronic® F127 gels in the presence of polyethylene glycols (PEGs) has been studied. All the PEGs studied raised T_1 *and lowered* T_2 *of 20% F127 gels; this effect was proportional to PEG concentration. At a certain critical "no-gel" concentration of PEG* (C_{ng})*, F127 lost its ability to form gels.* C_{ng} *was found to be inversely proportional to PEG molecular weight. An empirical relationship between* C_{ng} *and PEG molecular weight was obtained which can be used to predict effects of PEGs of any molecular weight on F127 gelation.*

INTRODUCTION

Polyethylene oxide-polypropylene oxide-polyethylene oxide (PEO-PPO-PEO) triblock copolymers, called poloxamers or Pluronics®, are nonionic surfactants that form clear, thermoreversible gels in water. These gels are of pharmaceutical interest because they can be used to modulate drug release based on temperature changes, and are being increasingly exploited for topical, transdermal, ophthalmic, and implantable applications (1–4). Pluronic® F127 (F127), which has a nominal molecular weight of 12,500 and a PEO/PPO ratio of 2:1 by weight, is the most widely used of the Pluronics in such pharmaceutical systems.

Schmolka (5) was the first to report that aqueous solutions of F127 above a concentration of 20% w/w are liquid at low temperatures, but gel upon warming to a certain critical gel formation temperature T_1. If the temperature is increased above T_1, two additional transitions are observed, first a gel melting (T_2) and then a cloud point (T_{cp}) (6). Thus, the system is a gel between T_1 and T_2, and a liquid at temperatures outside this range. The influence of additives such as inorganic salts, ethanol, and polyethylene glycol (PEG) 10,000 on T_1, of various Pluronic gels has been studied and changes in T_1 have been demonstrated (6–8).

We have recently shown (9) that many inorganic salts also reduce T_2 and T_{cp}, and that in some cases this re-

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sults in the loss of gelation. We have also reported that some cosolvents used in pharmaceutical F127 gels influence T_1 and T_2 (10). Such alterations of transition temperatures by additives may be undesirable in some instances, but could be exploited to design unique thermoresponsive drug delivery systems in other cases.

Recently, Malmsten and Lindman (11) reported that homopolymers such as PEO and PPO affect the gelation transitions of F127 gels. They examined the effect of PEO 6000 and PEO 20,000 and found that both caused the gel to melt at lower temperatures (i.e., T_2 was lowered). PEO 20,000 was more efficient at lowering T_2 compared to PEO 6000. At high PEO concentrations, no gel was observed. PPO, on the other hand, raised T_2 of the gels.

Preliminary observations in our lab indicated that the PEGs show behavior similar to PEO in such systems. Since PEGs are widely used in pharmaceutical formulations, their addition to F127 gels could be used to design gels of the desired transition temperatures. In particular, the role of PEG molecular weight in altering gel transitions was of interest. We decided to investigate the F127-PEG systems in greater detail, and to use the 20% F127 gels rather than the 25% gels used by Malmsten and Lindman, since 20% is the concentration used in most pharmaceutical formulations.

MATERIALS AND METHODS

Materials

Pluronic F127 (Pluracare® grade, gift from BASF), and PEGs 400–10,000 (Aldrich Chemical Company) 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.

F-127 Gel Preparation

Gels were prepared on a weight/weight basis by the cold method (5): F127 and PEG were weighed out and mixed with an appropriate quantity of water. The mixture was placed in a refrigerator until a clear, homogenous liquid formed. All the studies used 20% w/w F127.

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. Such visual observation techniques of determining gel formation temperatures have been commonly used for Pluronic gels (11,12), and give very reproducible results. We duplicated some experiments reported in the literature to validate our technique; these are discussed in the Results section. 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.

RESULTS AND DISCUSSION

Phase Diagram of the F127-PEG System

Figure 1 shows a typical phase diagram for an aqueous 20% F127 gel in the presence of various concen-

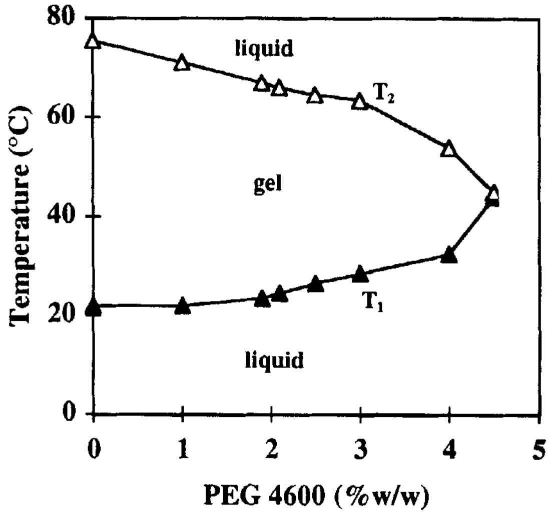

Figure 1. Effect of PEG 4600 on the gel formation (T_1) and gel melting (T_2) temperatures of 20% w/w F127 Pluronic gels. The T_1 curve is shown with solid triangles, and the T_2 curve with open triangles.

trations of PEG; this particular figure shows the behavior with PEG 4600 as an example. All the other PEGs studied behave similarly. The data show that PEG 4600 increases T_1 and decreases T_2. These two transition temperatures become essentially equal at a concentration of 4.5% w/w PEG 4600, and gels do not form in mixtures containing PEG 4600 concentrations of 4.5% w/w or greater. This concentration of 4.5% is termed the "no-gel" concentration for PEG 4600 in 20% F127 gels.

Effect of PEG Molecular Weight on Gelation

Figure 2 shows phase diagrams of F127 gels in the presence of PEGs of different molecular weights. Clearly, the higher the PEG molecular weight is, the smaller the region of F127 gel stability becomes. This result is in agreement with the results of Malmsten and Lindman (11), who studied 25% F127-PEO systems with PEO molecular weights of 6000 and 20,000. The higher molecular weight PEGs occupy a larger volume in solution and appear to be much more effective at disrupting the stability of F127 micellar aggregates, even at very low concentrations.

It is interesting to note the symmetrical nature of the profiles in Fig. 2. For any one PEG, the change in T_1 is about the same as the change in T_2. Also, the T_1 and T_2 profiles appear to meet at a temperature of about 47°C for all the F127-PEG systems studied. This indicates that the mechanism of effect of all the PEGs is the same; the difference is only the PEG molecular weight. We then looked for an empirical relationship between PEG molecular weight and its effect on F127 gelation. We define a PEG concentration, C_{ng} as the no-gel concentration; i.e., the PEG concentration at and above which 20% F127 systems will not gel. This is the concentration at which T_1 and T_2 are essentially the same. Since C_{ng} is inversely proportional to PEG molecular weight, we plotted C_{ng} versus 1/MW; the graph obtained is shown in Fig. 3. We obtain a straight line with the following equation:

$$C_{ng} = -0.765 + 2.627 \times 10^4/\mathrm{MW}_{PEG}$$

where C_{ng} is the no-gel concentration of MW_{PEG} is the corresponding PEG molecular weight. The correlation coefficient of the line is 0.998. This equation can be used to predict the behavior of 20% F127 gels in the presence of PEGs of any molecular weight between 1500 and 10,000.

The mechanism by which PEG alters T_1 and T_2 and thereby disrupts gel formation is not precisely known. Malmstem and Lindman (11) reviewed the various possibilities, and concluded that simple solvent polarity effects do not explain this behavior. Instead, osmotic pressure gradients, and the translational and conformational entropy of the PEG and F127 have to be considered. Our work has shown that there is a linear relationship between the no-gel PEG concentration and the reciprocal of the PEG molecular weight. This relationship can be used to predict the no gel concentration of any PEG one wishes to use in a F127 gel formulation. Using this, and the observation that the T_1 and T_2 profiles are symmetrical and meet at a temperature of about 45°C, one can construct an estimated phase diagram of

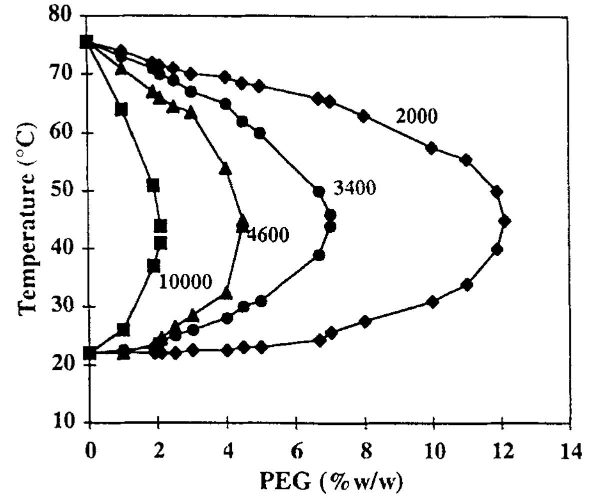

Figure 2. Phase diagrams of 20% Pluronic F127 gels in the presence of various concentrations of PEG 2000, PEG 3400, PEG 4600, and PEG 10,000.

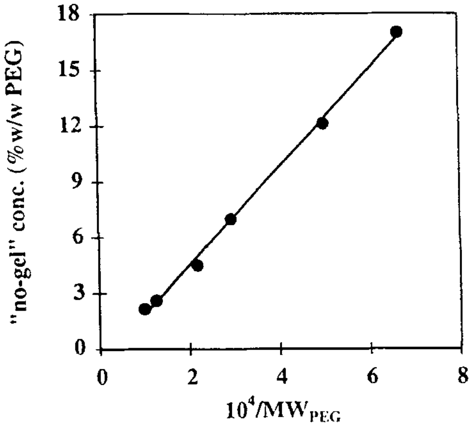

Figure 3. Relationship between the PEG no-gel concentration (C_{ng}) and PEG molecular weight for the gelation of 20% w/w Pluronic F127 gels.

any 20% F127-PEG gel system. This information should be useful in designing F127 gels with the desired gelation properties.

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