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Temperature-dependent rheological behavior of Pluronic F-127 aqueous solutions

Vincent Lenaerts [1], Caroline Triqueneaux [2], Michel Quarton [3], Françoise Rieg-Falson [2] and Patrick Couvreur [2]

[1] *Faculté de Pharmacie, Université de Montréal, Montréal, Qué. (Canada),* [2] *Laboratoire de Pharmacie Galénique et de Biopharmacie U.A. C.N.R.S. No 1218, Université de Paris XI, Chatenay-Malabry (France), and* [3] *Laboratoire de Chimie Minérale, Université Pierre et Marie Curie, Paris (France)*

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Summary

A rheological study of Pluronic F-127 aqueous solutions of 15–30% concentrations was undertaken at temperatures ranging from 15 °C to 35 °C. An exponential relationship was found between viscosity and temperature, with curve slopes depending upon Pluronic concentration. A theory is proposed to explain that phenomenon. It is based on the previously reported observation that pluronic micelles in water solution undergo a thermally induced swelling together with a desolvatation. The proposed hypothesis is, therefore, based on the creation of a cross-linked network. DSC and X-ray diffraction studies show this network consists of weak interactions (probably hydrogen bonds) accounting for the reversibility of the thermoviscosimetric behavior, and generates no preferential 3-dimensional arrangement.

Introduction

Pluronic F-127 is an ABA block copolymer of polyoxyethylene-polyoxypropylene (ratio 7 : 3), with a molecular weight of 12,500, more readily soluble in cold than in hot water (BASF Wyandotte, Report OS-796).

Concentrated aqueous solutions (20–30% w/v) of this polymer have been reported to show a dramatic increase in viscosity when heated from 5 °C to room or body temperature (Krezanoski, 1980).

This interesting characteristic has been exploited for the development of drug delivery systems such as burn dressings (Schmolka, 1972), long-acting eye droplets (Krezanoski, 1980), prolonged-release injectables (Collett et al., 1985), and, recently, as a sustained-release vehicle for the topical administration of anticancer agents (Miyazaki et al., 1984).

A study of lidocaine release from several ointments has shown that Pluronic F-127 gels allowed the highest diffusion coefficient of all tested formulations, including a 2% carbopol 940 gel, a 5% methocel 4000 gel, and commercial jellies and creams (Chen-Chow and Frank, 1981b).

Unfortunately, very few thermorheological studies of these colloidal systems have been pub-

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Correspondence: V. Lenaerts, Faculté de Pharmacie, Université de Montréal, C.P. 6128, Succursale A, Montréal, Qué., Canada, H3C 37J.

lished to date. Miller and Drabik (1984) have studied the viscosity of different types of Pluronics as a function of the concentration at two temperatures, while Chen-Chow and Frank (1981a) have published data on the viscosity of a 25% Pluronic-127 solution at different temperatures as a support to a study of the diffusion of model drugs in Pluronic solutions.

The absence of a detailed study of the rheological behavior of Pluronic F-127 solutions as a function of temperature may be partly responsible for the controversy that still exists concerning the gelation mechanisms of these colloidal systems.

Materials and Methods

Materials

Pluronic F-127 was purchased from Imperial Chemical Industries, Paris, France, and used without further processing.

Sodium chloride Rectapur (Prolabo, Paris, France) and distilled water were also used for the formulations.

Methods

Pluronic F-127 solutions ranging from 15 to 30% (w/v) were prepared by the cold method described by Schmolka (BASF Wyandotte Corp., no. 0-153). Some gels were prepared with the addition of 5% (w/v) sodium chloride.

Rheological studies were performed with the different solutions or vehicles thermostatized at temperatures ranging from 5 to 40 ± 1° C, using a rotating cylinder viscosimeter (Rheomat 30, Contraves, Zurich, Switzerland).

The rotation speed of the internal cylinder was adjusted to scan automatically from 3.5 (speed setting = 15) to 350 (speed setting = 30) RPM and back in exactly 60 s.

The viscosity of the samples was derived from the shear stress at 189.4 (speed setting 28 R.P.M.) using the following equation:

$$\eta = \frac{\tau_m \times \tau_u \times s}{\epsilon^\circ}$$

Where

τ_m = shear stress in % of the maximal observed value.

τ_u = geometrical coefficient allowing the expression of τ_m in mPa.

ϵ° = shear rate, a function of rotation speed and cylinders geometry.

s = sensitivity coefficient of the viscosimeter.

Differential scanning calorimetry studies were performed using a Microcalorimetre Differentiel 111, (Setaram, Lyon, France).

Samples of approximately 60–80 g gel were placed in open cells and accurately weighed. The cells were first thermostatized in the oven at −30° C. The temperature of the oven was then brought to +30° C at a heating rate of 3° C/min.

The heat flow (in mW) between the sample and the oven was recorded as a function of the oven temperature.

X-ray diffusion studies were performed with the 20% (w/v) sample placed in cells hermetically sealed by a berylium window. The cells were thermostatized between 20.0 and 35.0 ± 0.1° C. The X-ray spectra were obtained by the reflexion method using a diffraction goniometer (Philips PW 1050, Eindhoven, The Netherlands). The radiation used had the Cu K_α-wavelength selected by a Ni rear-filter.

Results and Discussion

In our experimental conditions, all solutions had a Newtonian behavior (example of the 20% solution at 20° C in Fig. 1), except for the more concentrated solutions whose behavior was observed to shift to pseudo-plastic and plastic when the temperature was increased (the 30% solution, for example, became pseudoplastic at 14° C and plastic at 24° C).

The viscosity of these solutions was plotted against temperature, giving rise to biexponential relationships (Fig. 2A, B).

The initial part of the curve is characterized by a decrease in viscosity which is probably explained by the rise in activation energy resulting from the increase in temperature. Such a phenomenon has, indeed, been described for most colloidal solutions

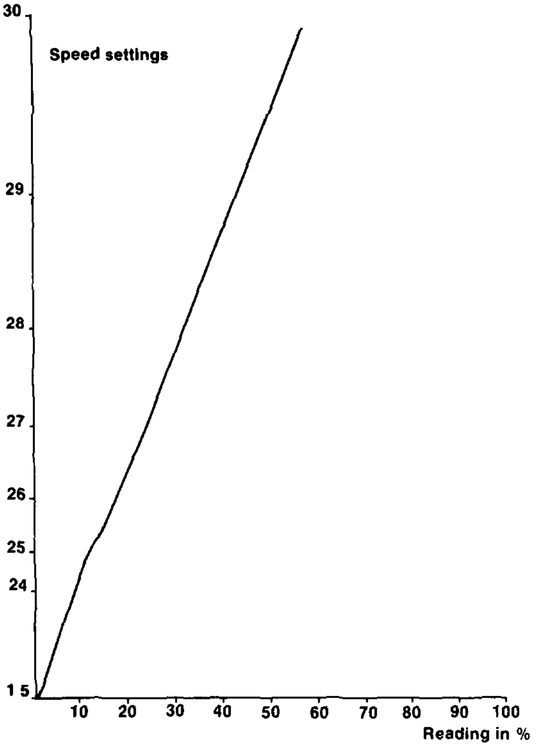

Fig. 1. Rheogram of a 20% (w/v) aqueous solution of Pluronic F-127 at 22° C.

(Fox et al., 1956), and is likely to apply to the present situation since the polymers are arranged in independent micelles (Prasad et al., 1979).

The phenomenon is considered as concentration-independent since the decrease rates appear similar (Fig. 2A). This independency is consistent with the mentioned theory based on the activation energy (Fox et al., 1956).

Contrarily, the second part of the curve shows an exponential increase in viscosity at a concentration-dependent rate. Such a relationship is not in accordance with the sol–gel transition mentioned in previous papers (Miller and Drabik, 1983; Vadnere et al., 1984). It is, however, consistent with some fundamental work on structural arrangement and thermodynamical behavior of Pluronic solutions, conducted by such authors as Attwood et al. (1985), Rassing and Attwood (1983) and Rassing et al. (1984). These authors have, indeed, concluded from ^{13}C-NMR, ultrasonic velocity and light-scattering studies that the

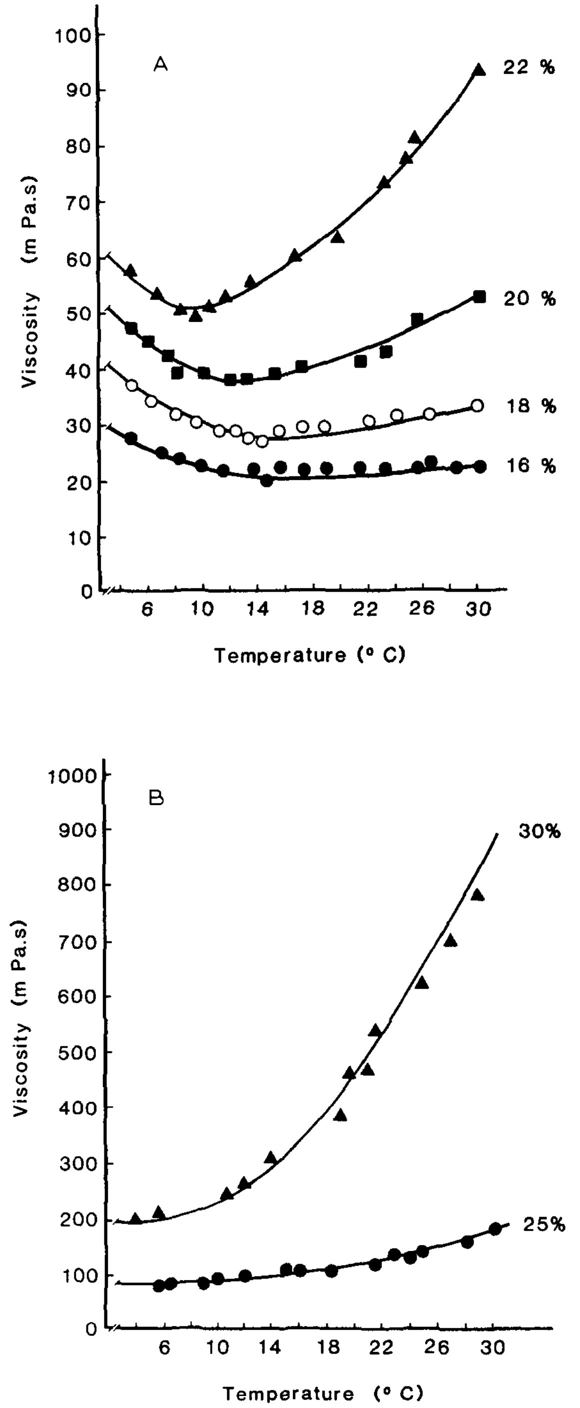

Fig. 2. A: viscosity of 16%, 18%, 20% and 22% aqueous solutions of Pluronic F-127 as a function of temperature. B: viscosity of 25% and 30% aqueous solutions of Pluronic F-127 as a function of temperature.

Pluronic micelles undergo a marked swelling upon heating. This swelling has been associated with conformational changes of the polymers due to temperature-related desolvatation. As a result, it is believed that polymers from different micelles eventually get in contact. A pseudo-cross-linkage is likely to appear then since the hydroxyl groups — made accessible by desolvation — have become capable of developing hydrogen and polar bonds.

Since both the desolvation and the swelling of the micelles evolve gradually with temperature, the presented hypothesis could account for the observation that the viscosity shows a progressive increase with temperature instead of the marked shift expected from a real sol–gel transition.

The concentration dependency was further analysed by plotting viscosity against concentration at given temperatures. Fig. 3 shows single exponential relationships characterized by temperature-dependent slopes.

This behavior is not surprising in view of the above-proposed theory. Indeed, enhancing the micelle concentration increases the number of possible cross-links and is thus likely to give rise to a more tight network characterized by a higher viscosity of the solutions.

For the same reason, when the concentration and the temperature are sufficiently high, the network becomes so tough that no shear rate can be generated when the lowest shear tensions are applied, explaining why the rheological behavior was observed to become plastic above 24°C for the 30% solution.

Likewise, a concentration enhancement reduces the intermicellar-distance, and consequently, the degree of micelle-swelling necessary for polymers to get into contact. The temperature at which the curve shifts from the concentration-independent decrease to the concentration-dependent increase should therefore be inversely related to the concentration. Such a relationship is, actually, evidenced by Fig. 2A when comparing the temperature associated to the minimal viscosity, particu-

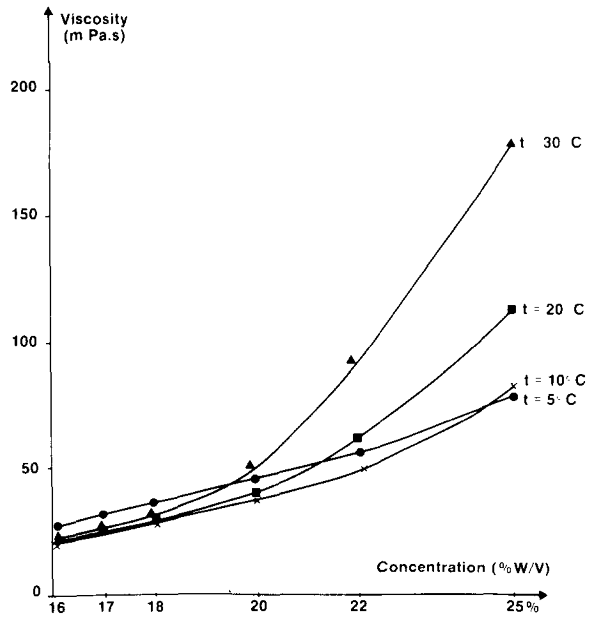

Fig. 3. Viscosity of Pluronic F-127 aqueous solutions thermostatized at 5°C, 10°C, 20°C and 30°C as a function of copolymer concentration.

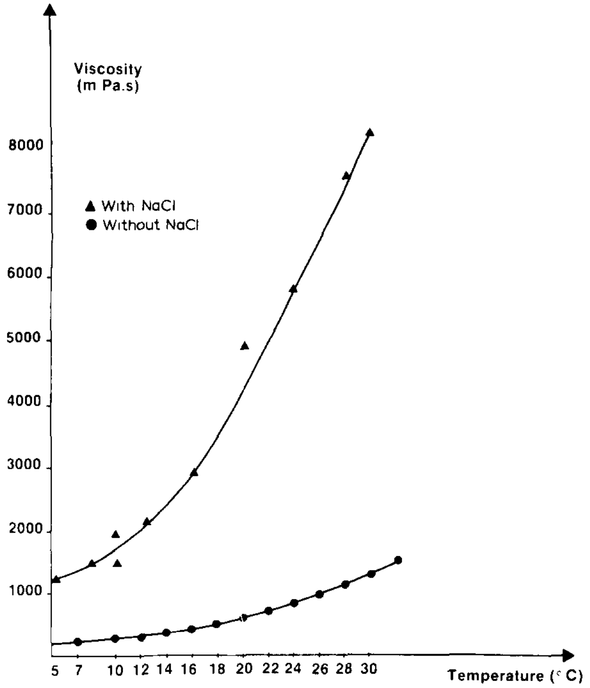

Fig. 4. Viscosity of a 30% (w/v) aqueous solutions of Pluronic F-127 with and without addition of 5% (w/v) NaCl as a function of temperature.

larly in the case of the 18, 20 and 22% solutions. For the more concentrated solutions, it is believed that this transition temperature was inferior to the studied temperature range.

Furthermore, if the proposed theory is valid, it is expected that increasing the ionic strength of the solution will bring the viscosity to increase more rapidly with temperature. Indeed, since part of the water will be engaged in ions solvation, the energy needed for achieving a given level of polymer desolvation will be reduced, and both the degree of micelle swelling .and the number of accessible hydroxyl groups at a given temperature will be increased. This hypothesis was confirmed by comparing the thermoviscosimetric behavior of a non-ionic 30% Pluronic solution to a 30% Pluronic solution containing 5% sodium chloride (Fig. 4). The latter shows, as expected, a sharper viscosity increase, very much in the same way as if the polymer concentration had been increased, in good accordance with the above-proposed theory.

Differential scanning calorimetry

Differential scanning calorimetry of the 20% Pluronic solution was performed between −30 °C and +30 °C, corresponding to viscosities of 45 and 52 m Pa.s respectively (with a minimum of 36 m Pa.s at 12 °C). No thermodynamic exchange was detectable in our experimental conditions, thus showing that the cross-links between the polymeric chains are generated by relatively weak interactions, probably hydrogen bonds and/or Van der Waals forces (Fig. 5).

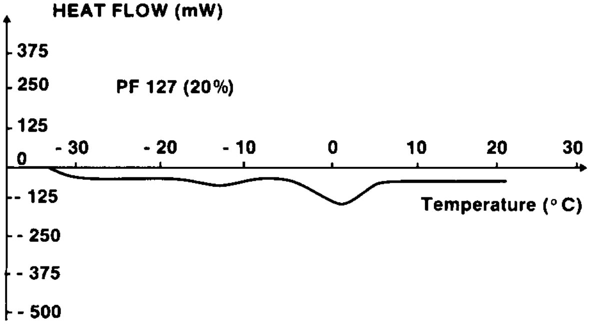

Fig. 5. Differential scanning calorimetry spectrum of a 20% (w/v) aqueous solution of Pluronic F-127.

It is probable that a sol–gel transition would have given rise to a detectable thermodynamic exchange, and, therefore, the DSC profiles are considered as consistent with the presented theory according to which the increase in viscosity results from the thermally induced cross-linking of the polymers as a result of desolvatation and micelle swelling.

Furthermore, since the interactions evidenced in this DSC study are of a reversible nature, that explains the observed reversibility of the thermoviscosimetric behavior of Pluronic solutions (Chen-Chow and Frank, 1981a).

X-ray diffusion

An X-ray diffusion study of the 20% Pluronic solution was performed at various temperatures in order to check the possibility of preferential 3-dimensional arrangements appearing upon gelation.

Fig. 6 shows the spectra at 20 and 35 °C, corresponding to viscosities of 41 and 59 m Pa.s, respectively.

Two maxima are observed on both spectra, at $\sin\theta \simeq 0.068$ and 0.153, corresponding to a diffusion pattern. Since the temperature had no effect on these peaks, it is concluded that the radial atomic function has remained constant over the tested temperature range.

Furthermore, no diffraction was detected at both tested temperatures, showing that no crystalline or pseudo-crystalline arrangement had been formed. In other words, the Pluronic solution was characterized by an equal variability in the probability of finding a given electronic density around a point. It is therefore assumed that the thermally induced cross-links are randomly distributed in space and give rise to no preferential arrangement.

These results' do not support the previous hypothesis that Pluronic micelles are arranged as liquid crystals in the gel state (Chen-Chow and Frank, 1981a; Chen-Chow and Frank, 1981b). This hypothesis had, indeed, been proposed in order to explain why the diffusion coefficient of model drugs in Pluronic solutions increases with temperature despite the enhancement in viscosity. These authors have concluded that, since the drug was supposed to circulate in water channels separating liquid crystals, the factors influencing their

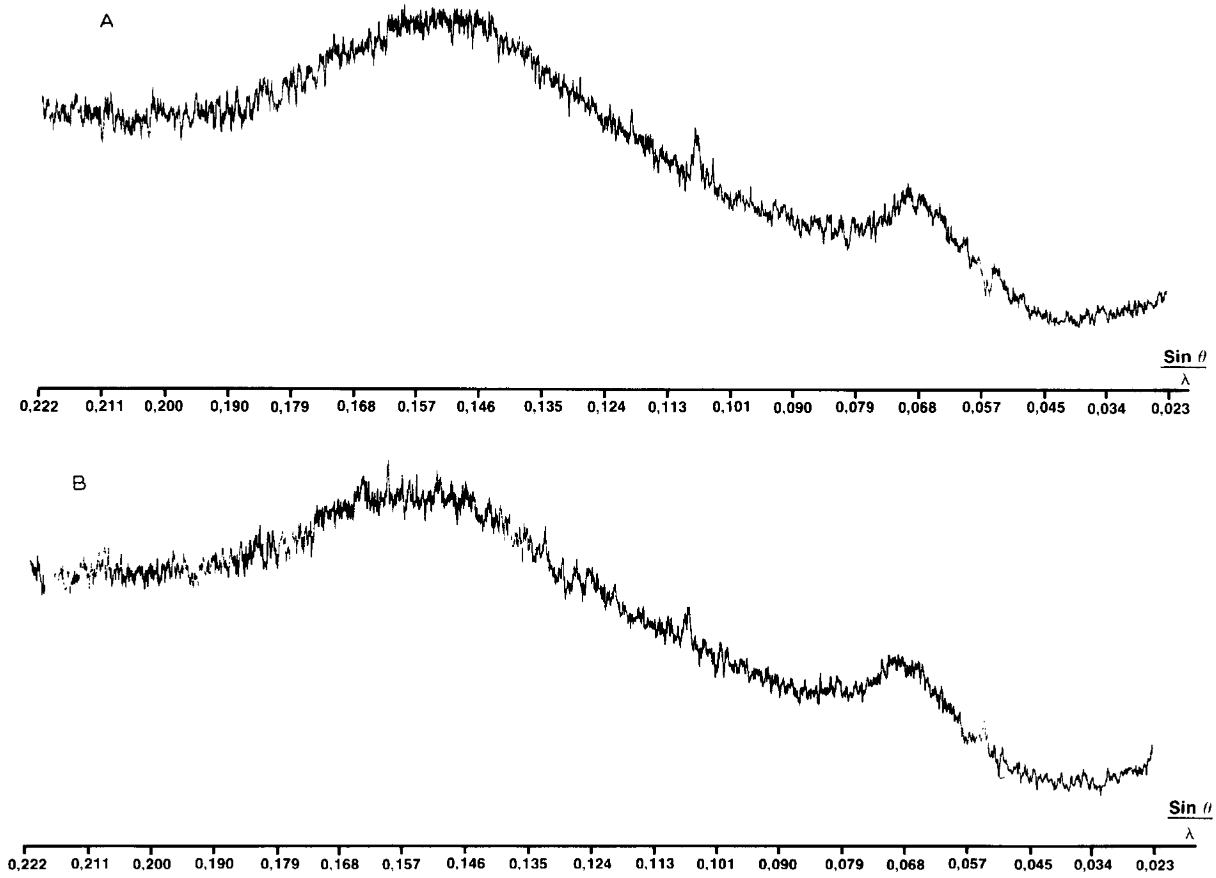

Fig. 6. X-ray diffusion patterns of a 20% (w/v) aqueous solution of Pluronic F-127 thermostatized at 20 ° C (A) and 35 ° C (B).

diffusion coefficient were only those related to the external water phase. The existence of these liquid crystals is challenged by our results.

Nevertheless, the general conclusion of Chen-Chow and Frank over the relationship between the diffusion coefficient and the external phase can still be considered as valid, provided the cross-linkage network has only a very minor influence on the diffusion-coefficient of the model-drugs. That would mean that the size of the pores created between the cross-links is relatively important, or, in other terms, that the created hydrogel shows such a high porosity that it has practically no influence on the diffusion of the tested model-drugs.

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References

Attwood, D., Collett, J.H. and Tait, C.J., The micellar properties of the poly(oxyethylene)—poly(oxypropylene) copolymer Pluronic F-127 in water and electrolyte solution. *Int. J. Pharm.*, 26 (1985) 25–33.

BASF Wyandotte Corp., *Technical data on pluronic polyols*, Publication #OS-796, Wyandotte, MI.

Chen-Chow, P.C. and Frank, S.G., *Act. Pharm. Suec.*, 18 (1981a) 239–244.

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

Collett, J.H., Tait, C.J., Attwood, D., Sharma, H.L. and Smith, A.M., In vivo evaluation of poloxamer gels as controlled release systems using scintigraphy. *12th International Symposium on Controlled Release of Bioactive Materials.* July 8th–12th (1985), Geneva, Switzerland.

Fox, T.G., Gratch, S. and Loshaek, S., Viscosity relationships for polymers in bulk and concentrated solution, in Eirich, F.R. (Ed.) *Rheology, Theory and Applications, Vol. 1*, Academic, New York, 1956, pp. 446–456.

Krezanoski, J.Z., *U.S. Patent 4, 188, 373*, Feb. 12th (1980).

Miller, S.C. and Drabik, B.R., Rheological properties of poloxamer vehicles. *Int. J. Pharm.*, 18 (1984) 269–276.

Miyazaki, S., Takeuchi, S., Yokouchi, C. and Takada, M., Pluronic F-127 gels as a vehicle for topical administration of anticancer agents. *Chem. Pharm. Bull.*, 32 (1984) 4205–4210.

Prasad, K., Luong, T.T., Florence, A.T., Paris, J., Vaution, C., Seiller, M. and Puisieux, F., *J. Colloid Interf. Sci.*, 69 (79) 225–232.

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

Rassing, J., McKenna, W.P., Bandyopadhyay, S. and Eyring, E.M., Ultrasonic and 13C-NMR studies on gel formation in aqueous solutions of the ABA block polymer Pluronic F-127. *J. Mol. Liq.*, 27 (1984) 165–78.

Schmolka, I.R., Artificial skin I. Preparation and properties of Pluronic F-127 gels for treatment of burns. *J. Biomed. Mat. Res.*, 6 (1972) 571–582.

Vadnere, M., Amidon, G., Lindenbaum, S. and Haslam, J.L., Thermodynamic studies on the gel–sol transition of some pluronic polyols. *Int. J. Pharm.*, 22 (1984) 207–218.