

# Investigation of Pluronic<sup>®</sup> F127–Water Solutions Phase Transitions by DSC and Dielectric Spectroscopy

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**ABSTRACT:** The water solutions of the block copolymers PEO<sub>n</sub>-PPO<sub>m</sub>-PEO<sub>n</sub>, known as pluronics, show a complex thermal behavior, since they are liquid at low temperature (5°C), and they can give soft gel when heated at body temperature (37°C). These properties are of great interest in biomedical applications. To properly design these applications, a prerequisite is the knowledge of the thermodynamics—how much—and of the kinetics—how fast—with which these transformations take place. In this work, solutions of F127 (the copolymer for which  $n = 100$  and  $m = 65$ ) were studied by varying the concentration and the temperature and analyzing their behavior when heated under several heating rates. The studies were per-

formed by differential scanning calorimetry (DSC) and dielectric spectroscopy. The investigations carried out under equilibrium conditions allowed us to determine the thermodynamics of the phase transitions, whereas the investigations carried out under varying conditions allowed us to quantify the kinetics of the phase transitions. Empirical models were also proposed to describe both the thermodynamics and the kinetics observed. © 2009 Wiley Periodicals, Inc. *J Appl Polym Sci* 114: 688–695, 2009

**Key words:** biological applications of polymers; block copolymers; dielectric properties; differential scanning calorimetry (DSC); gelation

## INTRODUCTION

### Background

The block copolymers PEO<sub>n</sub>-PPO<sub>m</sub>-PEO<sub>n</sub> constitute a class of biocompatible surfactants known as pluronics or poloxamers. Their amphiphilic nature is due to the PEO water-soluble chains and to the hydrophobicity of the PPO segment.

Their water solutions exhibit complex phase behavior with temperature. Starting from temperatures close to 0°C, the affinity between water and PEO segments decreases on heating, and the single chain of polymer in solution (the unimers) can aggregate building up micelles, the phenomenon of micellization. Further temperature increase can cause a close packing of the micelles, building up to a soft gel with interesting properties for biomedical applications, the phenomenon is noted as gelation.<sup>1,2</sup>

The pluronic F127 (PEO<sub>100</sub>PPO<sub>65</sub>PEO<sub>100</sub>), whose solutions of proper concentration (around 20% w/w)

give a gel at body temperature (37°C), is of particular interest in biomedical applications. e.g., its use is under consideration to cover the stents used in percutaneous transluminal angioplasty.<sup>1,2</sup> To do this, a liquid solution (at 5°C) must be pumped into a catheter, and it must gelate only in the proper position in the cardiac artery. To predict the solidification behavior, both the thermodynamics and the kinetics of the micellization and gelation must be known.

### State of the art

The complex phase behavior of the pluronic water solutions gained much attention from researchers in the past.

Alexandridis et al.<sup>3,4</sup> studied the micellization phenomena by fluorescent spectroscopy and by DSC, obtaining the micellization temperature as a function of the solution concentration for several pluronics and suggesting an entropy-driven micellization process.

Wanka et al.<sup>5</sup> obtained the phase diagrams for several pluronic water solutions by dynamic light scattering (DLS), SANS, and polarized microscopy, identifying the micellization and the gelation thermodynamics (i.e., the equilibrium conditions under

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which micellization and gelation take place). They also performed measurements of surface tension (to get the critical micellization concentration, i.e., the concentration at which the micellization occurs for a given temperature) and DSC experiments (to quantify and to localize the micellization and the gelation conditions).

Malmsten and Lindman<sup>6</sup> carried out C-NMR measurements of pluronic water solutions under conditions close to micellization, clarifying the role that the PPO and PEO segments play during the micellization phenomenon. They also built the phase diagram of the Pluronic F127, and they investigated the effect of several co-solutes on the phase stability.

Song et al.<sup>7</sup> suggested the use of dielectric measurements and of the Hanai equation to quantify the degree of volume filling occupied by the micelle. They also estimated the micellization temperature from a change of slope in the graph dielectric constant vs. temperature. Their approach has been followed in the present work to get similar information, under equilibrium as well as under nonequilibrium conditions.

Prud'homme et al.<sup>8</sup> used the SANS technique to investigate the F127 micellization/gelation. They observed the presence of geometrical entities with defined size (the micelles), the size of which was independent from temperature and solution concentration. Thus, they hypothesized that the gelation was due to the close packing of the micelle and not to micelle growth.

Lau et al.<sup>9</sup> investigated the Pluronic F108 micellization/gelation process by rheology and DSC. They observed the large endothermic peak due to micellization and the very small endothermic peak due to gelation. Furthermore, the elastic modulus measurements during solution heating allowed them to follow the gelation process. However, it is worth noting that the rheological measurements carried out during heating do not allow the direct evaluation of the gelation thermodynamics, since the data were gathered under conditions far from equilibrium.

Li et al.<sup>10</sup> studied the gelation of the F127 water solution by SANS and the Monte Carlo simulation method, with the aim of clarifying the role of the solvent in the process. They confirmed that a fraction of the water is bonded with the polymer, and this fraction plays a significant role in the gelation, increasing the bond strength between the PEO segments in the micelle corona.

Cabana et al.<sup>11</sup> analyzed the gelation of F127 water solutions by rheology, DSC, and FTIR. They observed the increase in viscosity during the heating caused by the gelation. They also confirmed the very small endothermic gelation peak and explained the minimal enthalpy effect as the transition of the last unimers that enters the micelle, which are closely packed to form the gel.

Mortensen and Talmon<sup>12</sup> studied water solution of F127. They confirmed the presence of a hard sphere by direct visual observation of vitrified specimen by cryo-TEM (cryogenic temperature transmission electron microscopy), and they quantified the volume fraction occupied by the sphere by SANS measurements.

Most of the work was thus done with the aim of clarifying the fundamentals of the observed phenomena. In particular, the thermodynamics of the phenomena have been widely investigated, whereas it should be emphasized that the kinetics of the phenomena have been neglected in the studied performed. However, for practical applications, it should be known to which extent—the thermodynamics—and with which rate—the kinetics—the phenomena develop. Therefore, an overall description of the thermodynamics and kinetics of micellization and of gelation still lacks, and it is highly desirable.

### Aim

Aim of this work was to observe and to quantify the thermodynamics and the kinetics of the micellization and gelation phenomena for F127's water solutions.

## MATERIALS AND METHODS

### Materials

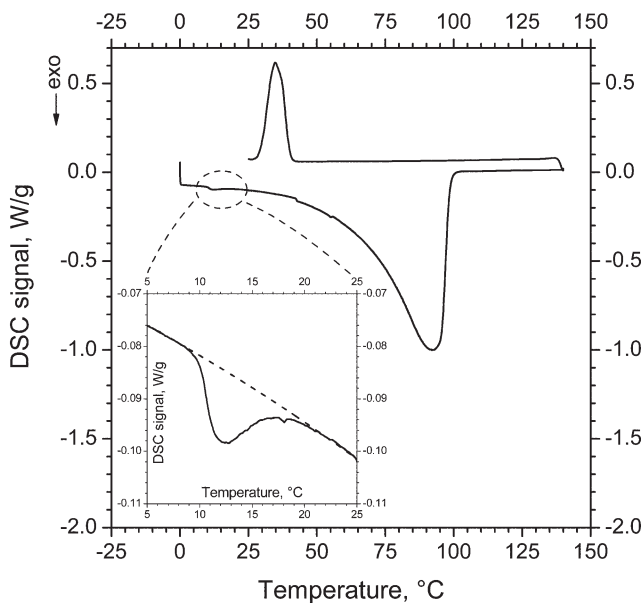
Pluronic F127 flakes (CAS no. 9003-11-6) were purchased from Sigma Aldrich (Milano, Italy). Solutions containing 10, 15, 20, and 22% w/w of the polymer were prepared by adding cold distilled water to the flakes, gently mixing, and allowing the stabilization, keeping them at 4°C overnight (cold method).

### DSC measurements

The DSC measurements were performed in a Mettler Toledo DSC 822, by heating the samples at 1°C/min. The heating rate was selected as a compromise between the need for a condition close to the equilibrium (heating rate as low as possible) and a signal/disturbance ratio acceptable (heating rate not too low). The signals were recorded and, after a properly designed baseline subtraction procedure, used to localize the micellization phenomenon.

### Dielectric constant measurements

The dielectric constants of the water/pluronic systems were measured in the frequency range 200 MHz to 6 GHz, using the network analyzer Agilent Network Analyzer mod. ES 8753, equipped with the coaxial probe mod. 85070D. The dielectric spectroscopy is a nondestructive analysis, requires short time to assay the values, and has a good repeatability.



**Figure 1** DSC signal recorded during the heating/cooling of a solution of F127 (20% w/w). Continuous line: DSC signal; dashed line: baseline. Temperature program: heating from 0 to 140°C at 1°C/min, holding at 140°C for 10 min, then cooling from 140°C to 20°C at 10°C/min. Inset: The zone where micellization and gelation take place, together with the baseline to be subtracted.

## RESULTS AND DISCUSSIONS

### Thermodynamics of micellization

The first phenomenon that takes place during pluronic water solution heating is the so-called micellization, i.e., the aggregation of polymer single-chain “unimers” to form micelles, with a central core built up of PPO hydrophobic segments and an external corona built up of PEO hydrophilic segments. The micellization is an endothermic phenomenon; thus it can be detected by a properly designed DSC test. In this work, small quantities—the order of 10 to 20 mg—of F127 water solutions were inserted in DSC sample holder, and then they were subjected to the following thermal history: heating at 1°C/min from 0 to 140°C, followed by a short staying at 140°C and then by a cooling to 25°C at 10°C/min. During the heating, the most important phenomenon—the one that requires the maximum amount of energy—is of course the water evaporation, with a peak around 100°C; during the cooling the polymer—which at this point is dry—gives up to the solidification with a related exothermic peak around 35°C. An example of such behavior is in Figure 1, for a F127 solution 20% w/w.

The micellization phenomenon takes place around room temperature, and it is noticeable as a very small shoulder on the large endothermic peak of water evaporation. To quantify the micellization, there is the need for a careful signal manipulation. The water evaporation peak was thus fitted by a proper function

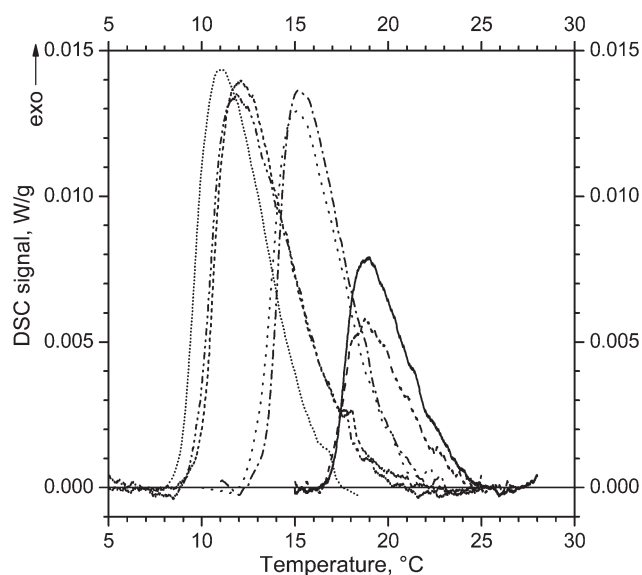
that plays the role of the baseline for micellization peak analysis. The region of interest and the baseline are emphasized in the inset in Figure 1. After the baseline fitting, this baseline was subtracted from DSC signal, giving the evolution of the signal as due only to the micellization phenomenon.

In Figure 2, the DSC signals were reported for several F127 concentrations, after baseline subtraction. The data were reported as positive if endothermic, i.e., the opposite of the data in previous figure, for a matter of convenience. For some concentrations, two signals were reported to confirm the data reproducibility. Peaks are due to the micellization phenomenon; thus from this graph the micellization temperatures were obtained as a function of solution concentrations. At higher concentrations, the signals show small shoulders at temperatures higher than the micellization ones: They can be assigned to the gelation phenomena, which require much less heat.

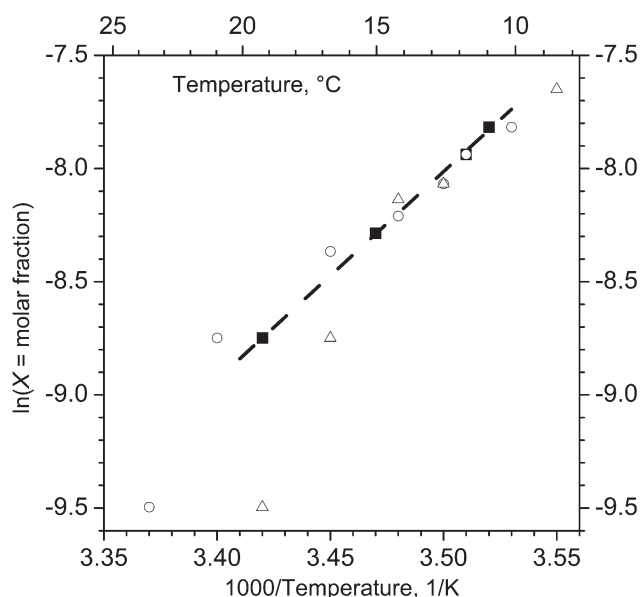
The molar fraction of F127 ( $X$ , which has a molar mass  $MM_{F127} = 12.6$  kg/mol) can be calculated from the weight/weight concentration  $C$ , as follows:

$$X = \frac{\frac{C}{MM_{F127}}}{\frac{C}{MM_{F127}} + \frac{1-C}{MM_{Water}}} \quad (1)$$

The molar concentration can then be drawn versus the micellization temperature (or versus the inverse of absolute micellization temperature). In Figure 3, the data obtained in this work (four data symbols,



**Figure 2** DSC signals, after baseline subtraction, for several F127 solutions. Runs are repeated to verify experiment reproducibility. Continuous and dashed line,  $C = 10\%$ ; dotted and dash-dotted line,  $C = 15\%$ ; dash-dot-dotted and short dashed line,  $C = 20\%$ ; short dotted line,  $C = 22\%$ . The large peaks are due to micellization; the small shoulders (for higher solution concentrations) are due to the gelation phenomenon.



**Figure 3** The micellization concentration (in term of molar fraction) versus the temperature (on the top axis) and versus the inverse of temperature (on the bottom axis). Data from literature are reported for comparison, and the data obtained in this work are linearly fitted, with a very good correlation coefficient. Full squares, this work, by DSC; open circles, Wanka et al., by DSC; open upward triangles, Song et al., by dielectric measurements.

closed squares) were reported in comparison with data taken from literature.<sup>5,7</sup> The data compare well, and they were very well described by an Arrhenius-like equation (dashed line):

$$\ln\left(\frac{X}{X_0}\right) = \frac{\Delta H}{R} \left(\frac{1}{T} - \frac{1}{T_0}\right) \quad (2)$$

In eq. (2), the reference value is ( $T_0 = 292 \text{ K} = 19^\circ\text{C}$ ,  $X_0 = 1.59 \cdot 10^{-4}$ , i.e.,  $C_0 = 10\%$ ), and the micellization enthalpy is  $\Delta H = 80.25 \text{ kJ/mol}$ ,  $R = 8.314 \text{ J/(K mol)}$  being the universal gas constant. Equation (2) is a first result of this work: For a given F127 solution, it allows the micellization temperature calculation.

The micellization could be viewed as an energy barrier-triggered phenomenon, i.e., the micelle formation takes place as soon as the free enthalpy of the micelle is lower than the unimers' one. It is reasonable to assume that the transport phenomena do not play a role in their formation (which takes place on the nanometric size scale); thus the micellization itself is a very fast process. Therefore, the (practically immediate) kinetics of the micellization is of no practical interest.

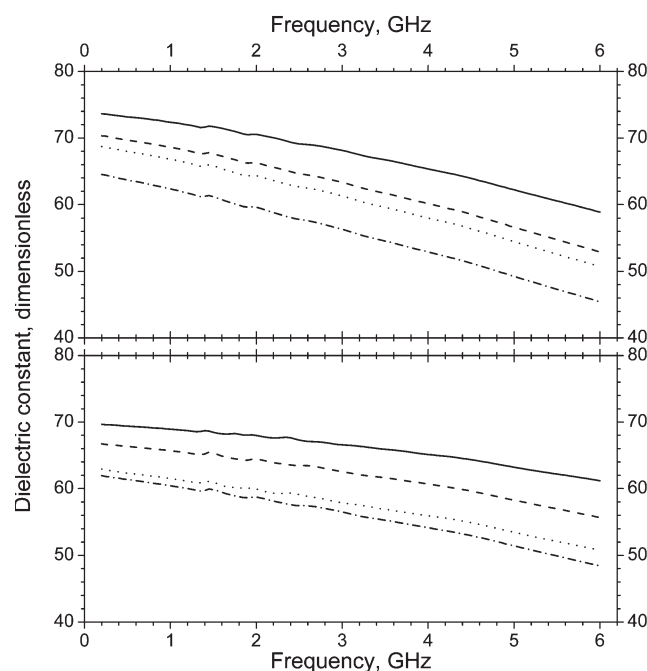
### Thermodynamics of gelation

The gelation phenomenon takes place on heating at temperatures higher than the micellization. It consists in both micelle growth and aggregation. A soft gel was obtained from F127 solutions as soon as the

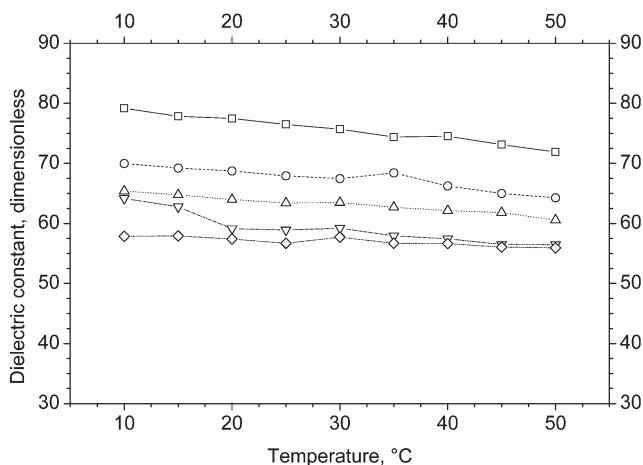
degree of space filling due to the micelles reaches the value of 52.3%, which corresponds to the critical degree of space filling for simple cubic packing of spherical particles. As already noted in DSC signal analysis, the gelation phenomenon is scarcely endothermic, thus it is hard to investigate it by calorimetry. Instead, the dielectric behavior (orientation and relaxation of polar structures under electromagnetic fields) of gel is different than the behavior of micelle solution; thus the dielectric spectroscopy (measurements of complex permittivity) has been found to be useful to carry out studies on gelation.<sup>7,13</sup>

The dielectric constant (the real part of the complex permittivity) values of F127 solutions as function of frequency are reported in Figure 4 for two different temperatures, 15 and  $30^\circ\text{C}$ . The dielectric constant is a decreasing function of frequency (the higher the electromagnetic wave frequency, the lower the time allowed to the dipole—the water molecule—to orientate with the electric field and then to storage energy) and it also decreases with F127 concentrations (since higher polymer content means less water, which contributes mainly to the dielectric constant of the solutions).

A single value of the dielectric constant, i.e., correspondent to a single frequency, is needed for the analysis of gelation phenomenon. The dependence of permittivity on frequency of F127 solutions is monotonic; thus the analysis will give the same result whatever frequency value is chosen as the



**Figure 4** Dielectric constant of several F127 solutions as function of frequency. Curves parameter is the solution concentration. Above, the graph at  $T = 15^\circ\text{C}$ ; below, the graph at  $T = 30^\circ\text{C}$ . Continuous line,  $C = 10\%$ ; dashed line,  $C = 15\%$ ; dotted line,  $C = 20\%$ ; dash-dotted line,  $C = 22\%$ .



**Figure 5** Dielectric constant at 2.45 GHz for several F127 solutions (and of the water) as a function of temperature. Continuous line and open squares, water; dashed line and open circles,  $C = 10\%$ ; dotted line and open upward triangles,  $C = 15\%$ ; dash-dotted line and downward triangles,  $C = 20\%$ ; dash-dot-dotted line and open diamonds,  $C = 22\%$ .

fundamental one. Since for technological reasons the most important frequency is 2.45 GHz (the value at which most microwave apparatuses work), this value was chosen as the fundamental frequency for the subsequent analysis.

The dielectric constant measurements were performed on F127 solutions stored under controlled low temperature ( $4^{\circ}\text{C}$ ) after their conditioning at the test temperature. Each test was carried out in triplicate, and the measurements were performed after allowing the sample enough time for stabilizing at the test temperature. Furthermore, the measurements were repeated after 1 h of conditioning to ensure that the thermodynamic equilibrium value has been measured, i.e., to be sure that the gelation process has reached the maximum extend compatible with the concentration and the temperature. Nine temperatures were investigated (10, 15, 20, 25, 30, 35, 40, 45, and  $50^{\circ}\text{C}$ ) for four concentrations (10, 15, 20, and 22%). The data—average of three measurements, after 1 h of conditioning at the test temperature—were reported as permittivity at 2.45 GHz versus temperature, with the concentration as the parameter, in Figure 5. The dielectric constant of distilled water was reported as a comparison. These data were the basis to get the degree of space filling, i.e., the measurement of the gelation extent. Indeed, the degree of space filling,  $\phi$ , could be calculated on the basis of Hanai's equation, as suggested by Song et al.<sup>7</sup>:

$$1 - \phi = \frac{\epsilon'_{\text{slz}} - \epsilon'_{\text{sphere}}}{\epsilon'_{\text{medium}} - \epsilon'_{\text{sphere}}} \left( \frac{\epsilon'_{\text{sphere}}}{\epsilon'_{\text{slz}}} \right)^{\frac{1}{3}} \quad (3)$$

In eq. (3), the Hanai's equation,  $\phi$  is the degree of space filling, which identifies the gelation as it

reaches the value of 52.3% (simple cubic packing of spherical particles);  $\epsilon'_{\text{slz}}$  is the dielectric constant of the F127 solution, as measured by dielectric spectroscopy;  $\epsilon'_{\text{medium}}$  is the dielectric constant of the medium that surrounds the micelles; and  $\epsilon'_{\text{sphere}}$  is the dielectric constant of the pure micelles (the spheres). All the dielectric constants must be evaluated at same frequency (2.45 GHz, as above reported). The measured value is  $\epsilon'_{\text{slz}}$ , the model aids to calculate the degree of space filling,  $\phi$ . Therefore, eq. (3) must have  $\epsilon'_{\text{medium}}$  and  $\epsilon'_{\text{sphere}}$  values to be used.

The medium that surrounds the micelles was made up the solution itself for temperatures lower than the micellization temperature (i.e., around the first micelles there is the solution itself until the micellization/gelation takes place). After the maximum packing of the micelles (after the gelation has reached its maximum extent, which Song et al.<sup>7</sup> located at  $50^{\circ}\text{C}$ ), the medium surrounding the micelles is made up of pure water. For temperature between the micellization one and the maximum packing one, the medium is made up of a solution with decreasing concentration, since unimers leave the medium to build up or to increase the size of micelles. Thus, the medium dielectric constant can be calculated by eq. (4):

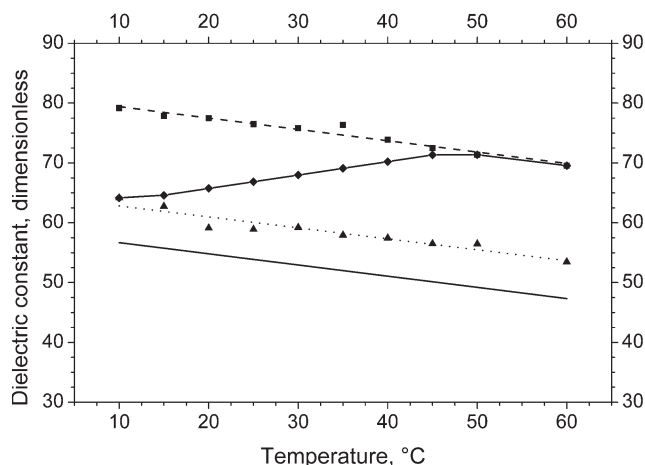
$$\epsilon'_{\text{medium}} = \begin{cases} T < T_{\text{mic}} & \epsilon'_{\text{slz}} \\ T_{\text{mic}} \leq T \leq T_{\text{packing}} & \text{"an average between"} \\ & \epsilon'_{\text{slz}} \text{ and } \epsilon'_{\text{water}} \\ T > T_{\text{packing}} & \epsilon'_{\text{water}} \end{cases} \quad (4)$$

To use eq. (3), the permittivity of the sphere must be known. A linear dependence from temperature can be postulated,<sup>7</sup> i.e.,

$$\epsilon'_{\text{sphere}} = a + bT \quad (5)$$

From DSC measurements (Fig. 2), the gelation takes place at  $17^{\circ}\text{C}$  for  $C = 22\%$  and at  $18^{\circ}\text{C}$  for  $C = 20\%$  (in agreement with the SANS measurements performed by Mortensen and Talmon<sup>12</sup>). Thus, the values for parameters  $a = 58.56$  and  $b = -0.187$  have been obtained by forcing eq. (3) to give  $\phi = 52.3\%$  (the gelation) at 20% and 22% for temperatures of  $18^{\circ}\text{C}$  and  $17^{\circ}\text{C}$ , respectively.

Figure 6 summarizes the data and the analysis required to get the degree of space filling by applying the Hanai equation (3). Both experimental permittivity data for water (full squares) and for F127 solution at 20% (closed triangles) were reported, along with the medium permittivity as obtained by eq. (4) (closed diamonds) and sphere permittivity as



**Figure 6** The different dielectric constant values used in Hanai analysis. The solution here is at 20% w/w of F127. Full squares, water; dashed line, water data linear fit; full upward triangles, solution; dotted line, solution data linear fit; continuous line, sphere; continuous line and full diamonds; medium.

calculated by eq. (5) (continuous line). All these dielectric constant values were reported versus the temperature. A graph similar to Figure 6 was obtained for each concentration investigated.

Applying the Hanai equation (3) to these data, the degree of space filling values were obtained as a function of temperature (in the range of 10 to 50°C) and concentration (in the range of 10 to 22%). These values are reported as symbols in Figure 7. The same graph reports, as lines, the predictions of an empirical model that is made up by eq. (6):

$$\phi(T, C) = \begin{cases} T < T_{\text{mic}}(C) & 0 \\ T \geq T_{\text{mic}}(C) & A(C) + \frac{0 - A(C)}{1 + \exp\left(\frac{T - T_{\text{mic}}(C) - a_1}{a_2 C + a_3}\right)} \end{cases}$$

with  $A(C) = (a_4 C + a_5) \left[ 1 - \exp\left(-\frac{T}{a_6}\right) \right]$

(6)

In eq. (6), the temperature is in Celsius and the concentration in w/w. The six parameters in eq. (6) have the values:  $a_1 = 3.58$ ,  $a_2 = -79.02$ ,  $a_3 = 17.385$ ,  $a_4 = 3.098$ ,  $a_5 = 0.0357$ , and  $a_6 = 10.837$ ; and they were obtained by regression from experimental data (by minimization of sum of square error = 0.0764, with Pearson's correlation coefficient of 0.8188).

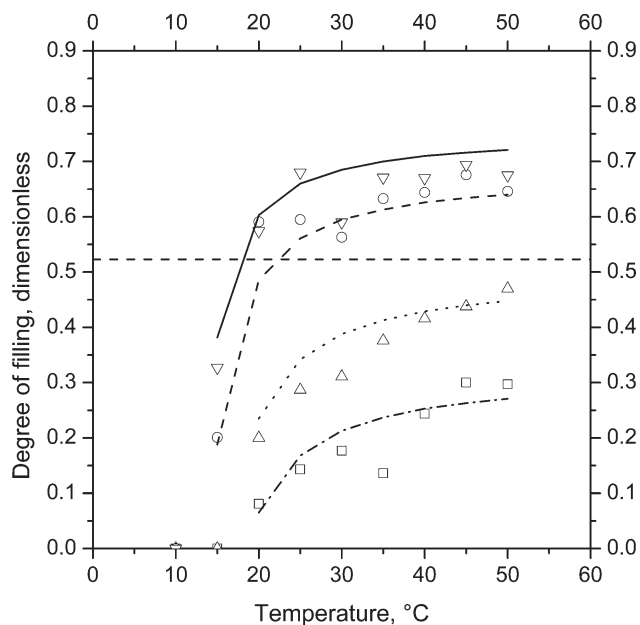
Equation (6), in which  $T_{\text{mic}}(C)$  is given by eq. (2), is another result of this work: For a F127 solution of concentration  $C$ , at a given temperature  $T$ , eq. (6) allows to calculate the degree of space filling  $\phi$ , and if it is not less than 52.3%, it means that in these condition the solution is a soft gel.

Both the Figure 7 and eq. (6) rightly show that the gelation process is not allowed for concentrations of

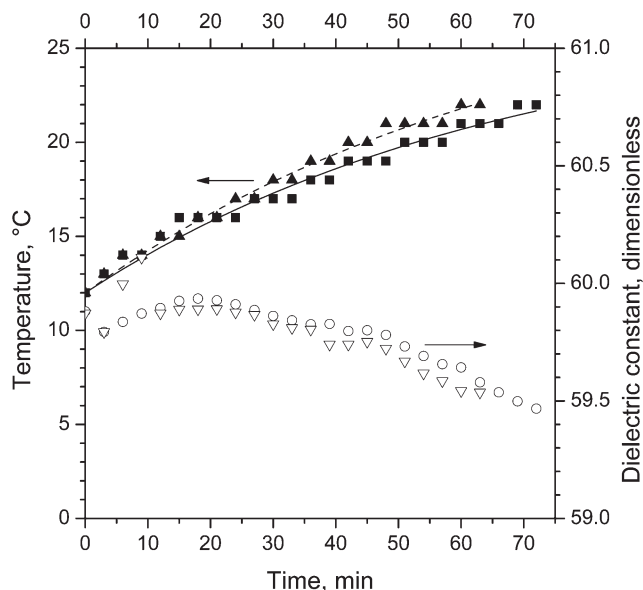
10% and 15% for all the temperatures investigated. Otherwise, for higher concentrations, namely 20% and 22%, the gelation takes place, respectively, at 22°C and 18°C, accordingly with rheological measurements, as reported by Grassi et al.<sup>14</sup> It is worth noting that rheological measurements in temperature sweep are performed under nonequilibrium conditions (involving a heating rate), thus not allowing discernment thermodynamic from kinetic aspects. However the gelation temperatures obtained by dielectric spectroscopy nicely match with rheological measurements, as reported by Lau et al.<sup>9</sup> and Grassi et al.<sup>14</sup>

### Kinetics of gelation

It is worth noting that eqs. (2) and (6) are models of a certain practical interest, since they allow us to predict the micellization and the gelation phenomena for F127 solutions as functions of concentration and of temperature. They were tuned and thus they can predict only equilibrium situations, i.e., they were useful in descriptions of the thermodynamics for these systems. Very often, the real process in which the F127 solutions were used involves a heating step (to build up the soft gel) or a cooling step (to liquefy the gel), during which the system experiences situation far from equilibrium. It has



**Figure 7** The equilibrium degree of space filling as function of temperature for F127 solutions at different concentrations. The value of 52.3% (the horizontal line) identifies the gelation point. Symbols are experimental data; lines are model predictions. Open squares and dash-dotted line,  $C = 10\%$ ; open upward triangles and dotted line,  $C = 15\%$ ; open circles and dashed line,  $C = 20\%$ ; open downward triangles and continuous line,  $C = 22\%$ .



**Figure 8** Temperature (on the left axis) and permittivity (on the right axis) evolutions with time during two heating runs (tests no. 2 and 3), for a 20% w/w water solution of F127. Full squares and continuous line, temperature for test 2; full upward triangles and dashed line, temperature for test 3; open circles, dielectric constant test 2; open downward triangles, dielectric constant test 3.

already been noted that the kinetics of micellization do not have a practical interest because once the micelles have been produced, the time delay in the soft gel production can be fully ascribed to the gelation process. Thus, whereas the kinetics of micellization could be assumed to be too fast to be observed and thus is not useful to investigate, it is of great importance to quantify the kinetics of gelation.

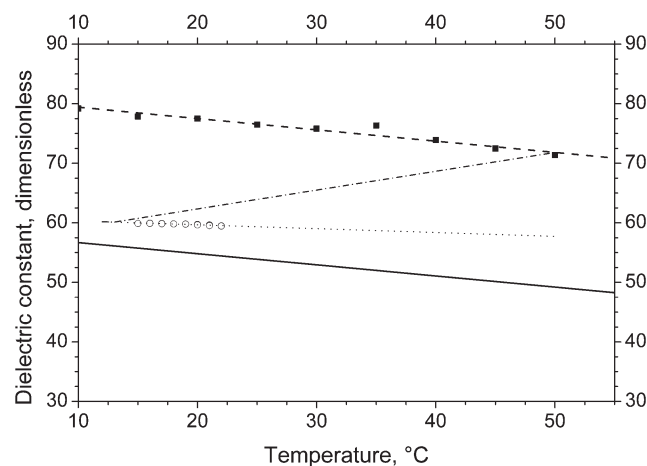
To investigate the kinetics of gelation, the dielectric measurements were performed during controlled heating runs, recording the permittivity at 2.45 GHz and the temperature evolution with time. The heating was accomplished by a water thermal bath, and thus only a limited range of temperatures and of heating rates can be explored. The measurements were carried out only on F127 solutions with  $C = 20\%$ , and the results of two tests are reported in Figure 8. The temperature evolution can be read on the left axis, whereas the permittivity evolution can be read on the right axis. During the two tests, the samples experiences practically the same thermal history, and since the permittivity measured is practically the same, the reproducibility of the data was assessed (only one example was reported, but the experiments were carried out in triplicate for each test, giving similar results).

The thermal history experienced by the sample during an heating run obtained simply inserting the sample itself in a thermostatic bath can be described by solving the lumped energy balance, obtaining:

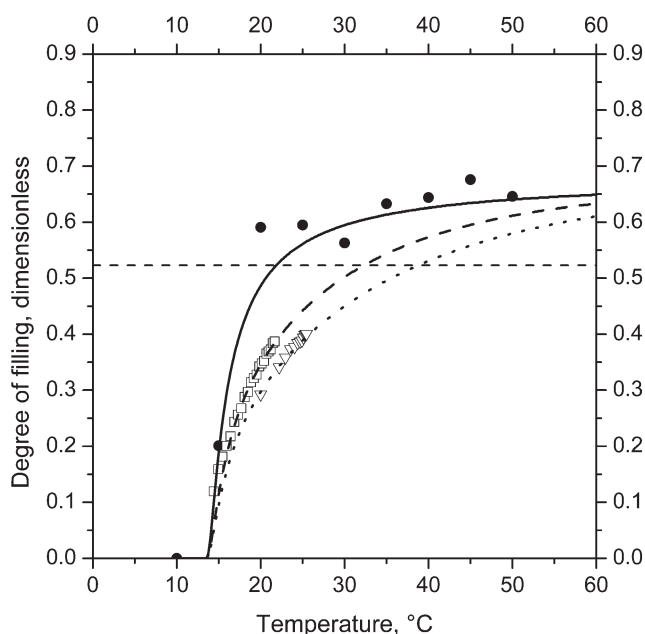
$$T(t) = T_{\infty} + (T_0 - T_{\infty}) \exp\left(-\frac{t}{\tau}\right) \quad (7)$$

In eq. (7), the parameters are: the initial temperature,  $T_0$ ; the asymptotic value,  $T_{\infty}$  (the bath temperature); and the time constant,  $\tau$ . The heating rate is not constant during this kind of test; however, to simplify the forthcoming analysis, a single parameter able to describe how fast the sample was heated during a test is highly desirable. Differentiating eq. (7) it is straightforward to obtain the heating rate  $\dot{T} = -(T - T_{\infty})/\tau$ , thus the heating rate is related to the ratio  $T_{\infty}/\tau$ , which can be taken as the single parameter needed for the subsequent analysis.

In Figure 9, data of dielectric constant versus temperature, obtained from the same “test 2” mentioned above, were reported in the same kind of graph of Figure 6, with the aim of performing the Hanai analysis. The dielectric constants of the water and of the micelle were supposed to be independent of the heating rate. Thus, the application of Hanai equation (3) allowed us to get the evolution of the degree of space filling (i.e.,  $\phi$  as function of the time). Since the thermal history is known, the data can be translated to a function of temperature. In this way, the degree of space filling during two heating runs are reported in Figure 10 as opened symbols. The open squares were obtained during a low heating rate run ( $T_{\infty}/\tau = 0.397^{\circ}\text{C/s}$ ) and the opened triangles during faster heating runs ( $T_{\infty}/\tau = 2.059^{\circ}\text{C/s}$ ). In the same graph, the equilibrium data for the 20% solution were reported as full symbols, along with the prediction of eq. (6) (the continuous line). It is worth noting that the degree of space filling during a heating run is lower than the value obtained at same



**Figure 9** The data for Hanai analysis during heating of a 20% w/w water solution of F127 (test no. 2). Full squares, water; dashed line, water data linear fit; open circles, solution; dotted line, solution data linear fit; continuous line, sphere; dash-dotted line; medium.



**Figure 10** The nonequilibrium degree of space filling for a 20% w/w water solution of F127, compared with the equilibrium data. Horizontal dash-line identifies the 52.3% value.

temperature but under equilibrium conditions. It means that the gelation phenomenon requires some time to take place. Having in mind a biomedical application that could require the injection into a body, a 20% solution of F127, which under thermal equilibrium gives a gel at 18°C, can be kept in liquid phase also at higher temperature (e.g., during the injection, if the heating rate is high enough). The last step, to obtain a full—even if empirical—model for micellization and gelation, is to write a mathematical tool able to predict the kinetics of gelation. A potential model is the following:

$$\phi(T(t), C) = \phi_{\text{eq}}(T, C)f(T(t))$$

$$\text{with } f(T(t)) = 1 - \exp\left[-\frac{T(t)}{b_1(T_\infty/\tau)^{b_2}}\right] \quad (8)$$

In eq. (8), the equilibrium value for the degree of space filling,  $\phi_{\text{eq}}$ , was obtained by eq. (6), and the function  $f(T(t))$  was built in analogy to the Avrami equation, commonly used to describe the nucleation and growth kinetics of crystalline solids. The two parameters of the model,  $b_1$  and  $b_2$ , must be estimated by comparison with experimental data. Equation (8) best-fitting values are reported in Figure 10 as dashed and dotted lines, and from the tuning procedure the values  $b_1 = 19$  and  $b_2 = 0.17$  were obtained.

In conclusion, eqs. (2), (6), and (8) allow description of the thermodynamics of micellization and gelation and the kinetics of gelation for water solutions of F127.

## CONCLUSIONS

In this work, the thermal behavior of Pluronic F127 water solutions was investigated by calorimetry and dielectric spectroscopy. The micellization phenomenon was observed by DSC analysis, successfully compared with literature data, and its thermodynamics was properly quantified. The gelation phenomena, scarcely noticeable during calorimetric tests, were investigated by dielectric spectroscopy, both under equilibrium and nonequilibrium conditions. The equilibrium data allowed the quantification of the thermodynamics of gelation, whereas the nonequilibrium data were used to quantify the kinetics of gelation. All the data observed were also described on the basis of empirical models.

The knowledge of thermodynamics and kinetics of phase change for these systems constitutes a powerful tool for designing and for managing biomedical applications of the pluronic water solutions. Indeed, by using the models proposed in this work, one can predict how fast—and to what extent—a solution of F127, initially cold and liquid, can give the gel when subjected to heating (the heating being due to the contact with the body).

Furthermore, the methods adopted in this work could be used to study the behavior of different pluronic water solutions or of more complex systems (e.g., solutions of F127 carrying a drug or different molecules).

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