Carbohydrate Polymers 82 (2010) 363–369

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Following HPMC gelation with a piezoelectric quartz crystal

M.I.S. Veríssimo[a], A.A.C.C. Pais[b], M.T.S.R. Gomes[a,*]

[a] CESAM/Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
[b] Chemistry Department, University of Coimbra, 3004-535 Coimbra, Portugal

ARTICLE INFO

Article history:
Received 2 November 2009
Received in revised form 19 April 2010
Accepted 26 April 2010
Available online 23 May 2010

Keywords:
HPMC
Water-soluble polymer
Thermal properties
Gel
Piezoelectric quartz crystal

ABSTRACT

The reversible thermal gelation of HPMC is the basis for many applications. A simple, fast and low-cost thermal characterization is important for manufacturers in order to choose the appropriate thermal conditions for each purpose and to avoid undesired changes in rheological properties when HPMC solutions are subjected to temperatures above that of gelation. In this work, a simple piezoelectric quartz crystal, without any coating, was used to monitoring the changes in the physical properties of several HPMC solutions when submitted to different thermal conditions. The technique allowed to follow the gelation process from its beginning. Submitting the HPMC solution to consecutive thermal cycles allowed to conclude on the reversibility of the overall process and of the physical changes induced by temperature. Inductance and resistance measurements are strongly dependent on the absolute value of temperature, above or below gelation, and reflect the changes on the properties of the HPMC solution.

1. Introduction

Thermoreversible gelation of aqueous solutions of macromolecules has been recognized as a highly important phenomenon which influences several practical applications of these materials. Hydroxypropyl methylcellulose (HPMC), a water-soluble cellulose derivative that gels at high temperatures, is often used as a multipurpose food ingredient (Burdock, 2007) and is the most important hydrophilic carrier material used in controlled drug delivery systems (Hardy et al., 2007; Siepmann & Peppas, 2001). Its popularity as a hydrophilic matrix derives from its non-toxic nature, its ability to accommodate a large percentage of drugs and negligible influence of the processing variables on drug releasing rates (Conti et al., 2007).

Despite the large amount of published work on the study of drug release from delivery systems based on HPMC, there is still a lack of knowledge and clarification of these phenomena. Siepmann and Peppas (2001) reviewed the large spectrum of mathematical models developed to describe drug release from HPMC-based controlled system devices, noting that complexity of mechanistic theories must increase whenever there is a need for reliability and more detailed information. Chirico, Dalmoro, Lamberti, Russo, and Titomanlio (2007) have focused on the transport phenomena for pure HPMC tablets, and found that their experimental data could be reproduced with a model already used in the literature. Barba et al. (2009a) developed an experimental method to measure the water and drug mass fraction along the radial profiles in immersed tablets. Despite these many studies, any work that allows to obtain a deeper insight on the HPMC structure and thermodynamic behaviour, either by applying new methods of observation, or by developing models based on previous observations will be important to the full characterization of such a complex matrix.

HPMC consists of hydroxypropyl and methyl groups on cellulose chains, and has the ability to gel when heated and melt when cooled. When the HPMC aqueous solutions are heated, the water structure breaks down with an increase in entropy, allowing the hydrophobic patches to interact, which leads to gelation. However, the gel system formed via hydrophobic associations can be affected by several factors, such as the number of aggregates per unit volume present in the system, the average size of the hydrophobic moieties, the structure of junctions, and the association strength (Li et al., 2001). Therefore, it is extremely difficult to control the network structure in the gel.

According to Kita, Kaku, Kubota, and Dobashi (1999), the HPMC aqueous solution has two characteristic temperatures: a lower critical solution temperature (LCST), where the polymer solution shows clouding or precipitation, and a thermal gelation temperature (TGT) at which the polymer solution exhibits a phase transition. This temperature-induced phase transition is known to be thermoreversible. The study of the HPMC reversible gelation process is complicated by the occurrence of other phenomena during the heating cycle and, so far, results do not have universal agreement (Hussain, Keary, & Craig, 2002). The gelation process could be studied by several different techniques, which in turn provides different definitions for the gelation temperature, rend-

---

* Corresponding author. Tel.: +351 234370722.
E-mail address: mtgomes@ua.pt (M.T.S.R. Gomes).

0144-8617/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2010.04.064

ing difficult to find consistent values in the literature (Liu, Joshi, Lam, & Tam, 2008).

A significant part of previous work relies on the use of different rheological experiments (Desbrières, Hirrien, & Ross-Murphy, 2000; Hussain et al., 2002), even for situations in which phase separation is observed and consequent technical difficulties may arise.

The rheological approach is considered the most direct and reliable way for determination of the sol–gel transition and characterization of rheological properties of gels, giving information about storage modulus (G'), loss modulus (G'') and viscosity (η) (Desbrières et al., 2000; Silva et al., 2008). Although, gelation can be detected by a sharp increase in viscosity (Sarkar, 1995) this method by itself it is not sufficient for thermo-gelation characterization frequently requiring other techniques to complement the information essentially to gain detail at the molecular level. These include UV/Vis spectroscopy (Silva et al., 2008; Xu, Song, Ping, Wang, & Liu, 2006) and macroscopic examination (Hussain et al., 2002) for cloud point determinations, small-angle neutron scattering and dynamic light scattering techniques to examine network formation and gel structure (Kobayashi, Huang, & Lodge, 1999), microcalorimetry to measure the exothermic heat of hydration (Li, 2002; Sarkar & Walker, 1995), fluorescence (Nilsson, 1995; Ridel, Evertsson, Nilsson, & Sundelöf, 1999) or ^{13}C NMR, wide-angle X-ray diffraction, environmental scanning electron microscopy, atomic force microscopy (Weng, Zhang, Ruan, Shi, & Xu, 2004), infrared spectroscopy (Bajwa, Sammon, Timmins, & Melia, 2009) for characterizing molecular interactions and many more.

Calorimetric techniques are useful essentially in characterizing the gelation phenomenon when variations are introduced in the system, e.g. in the degree of substitution, type of polymer or concentration (Desbrières, Hirrien, & Rinaudo, 1998; Ford, 1999). They are not adapted for the continuous monitoring of the evolution in solutions as temperature is increased, since their focus are localized phase changes.

Several authors have already used acoustic wave sensors for polymer studies, namely for polymer shear modulus determination (Bund, Chmiel, & Schwitzgebel, 1999; Holt, Gouws, & Zhen, 2006; Lucklum & Hauptmann, 1997), for monitoring polymer degradation (Sabot & Krause, 2002) or to study the viscoelastic changes that occur during the polymerization of acrylamide solutions (Reddy, Jones, & Lewis, 1997). However, the characterization of HPMC solutions, during temperature changes, has not been reported so far.

The thickness shear mode quartz crystal resonator, commonly consisting of a thin AT-cut quartz plate with two metal electrodes on both surfaces, is a sensitive device that can be used to characterize the mechanical behaviours of materials bounded on its surface. Frequency of oscillation of quartz crystals in liquids was shown to be affected not only by the density but also by viscosity (Nomura & Minemura, 1980; Nomura & Okuhara, 1982). The equation of Bruckenstein and Shay (Bruckenstein & Shay, 1985) shows that the observed frequency shift (Δf/Hz) is proportional to the square root of the product of density (d_l/g cm^{-3}) and viscosity (η_l/g cm^{-1} s^{-1}):

$$\Delta f = -2.26 \times 10^{-6} n f^{3/2} \sqrt{\eta_l d_l} \qquad (1)$$

where f/Hz is the series resonance frequency and n is the number of faces of the crystal in contact with the liquid ($n = 1$ or 2), the constant 2.26×10^{-6} Hz^{-1} g^{-1} cm^2 was calculated for an AT quartz crystal. Viscosity is a fundamental parameter in polymer characterization, in that it has a close relationship with the molecular weight and distribution of the polymer.

The piezoelectric quartz crystal is not fully characterized just by the series resonance frequency. Using the proper equipment, it is possible to measure not only the series resonance frequency but also the frequency at minimum and maximum impedance, the parallel resonance frequency, impedance and phase of impedance, among others. The electrical impedance of the quartz crystal can be described in terms of an equivalent electrical circuit (Martin, Granstaff, & Frye, 1991). The motional arm of this equivalent electric circuit is described by the capacitance (C_m), that represents the quartz mechanical elasticity, the inductance (L_m), that represents the inertial mass and the resistance (R_m), that represents the energy dissipation due to internal friction and damping from the crystal mounting. Loading the crystal with a liquid or gel changes the motional electrical parameters of the equivalent circuit. It should be noted that, while the addition of an ideal mass layer only affects the inductive component, fluid properties affect both inertial mass and viscous damping, which are translated into a change in both L_m and R_m (Bandey, Martin, & Cernosek, 1999). Therefore, as the analysis of the impedance spectrum of the acoustic wave sensor can be used to detect changes in the material properties of the layer in contact with the resonator, due to the disturbance in the propagation of the acoustic wave through the device (Holt & Gouws, 2004), this methodology is now applied to the study of HPMC solutions in an attempt to accurately define and establish the gelation temperature, as well as to elucidate some of the phenomena observed with temperature changes. In fact, the technique provides some unique features: real time monitorization, a very inexpensive methodology to detect gelation temperature by the monitorization of the series frequency of oscillation, and an insight into the structural changes of HPMC promoted by temperature changes, when quartz crystal equivalent electrical circuit inductance and or resistance are recorded. Besides, as the quartz crystal vibrates at much higher frequency (9 MHz) than the shear frequency used in dynamic rheological measurements, the HPMC system experiences a much smaller shear induced perturbation than the one occurring in the rheological experiments, where breaking of the weaker gel network bonds are prone to take place induced by shear stress (Kudryashov, Hunt, Arikainen, & Buckin, 2001). Although the in depth penetrations of the shear wave in the HPMC solution decrease with the frequency of oscillation of the quartz crystal, at 9 MHz it is still larger than the aggregates and therefore, one can expect the value of viscosity at this frequency to be closer to that at lower frequencies (Kudryashov et al., 2001). However, as the crystal/HPMC interface is included in the window of observation, it cannot be excluded the possibility that the results are reflecting the special properties at the interface, which may differ from the ones in the bulk of the HPMC solution (Reddy et al., 1997).

2. Experimental

2.1. Reagents

The cellulose derivative HPMC (Methocel® K15M Premium), 19–24% methoxyl and 7–12% hydroxypropyl, $M_w = 4.3 \times 10^5$ Da was purchased from Dow Chemical Company and was used without further purification. Milli-Q water was used as solvent.

2.2. Apparatus

Fig. 1 shows the home-made Teflon cell with the piezoelectric quartz crystal. The quartz crystal was placed between two o-rings and both parts of the cell were screwed. The HPMC solution was placed in the Teflon cell reservoir, in contact with one face of the piezoelectric quartz crystal.

Fig. 2 shows the experimental setup used for HPMC characterization. A thermostatic chamber Friocell 55 was used to control the temperature. The Teflon cell was placed inside the thermostatic chamber and a Pt100 temperature sensor was placed inside the Teflon cell reservoir, in contact with the HPMC solution, in order to measure the exact temperature of the HPMC solution. The Teflon

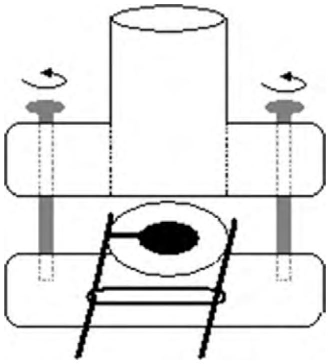

Fig. 1. Teflon cell with a piezoelectric quartz crystal.

cell was kept closed with a septum. The piezoelectric quartz crystal was connected to a home-made oscillator, connected to a Fluke PM 6685 frequencymeter, and to a 5 V power supply.

For impedance measurements, the experimental setup shown in Fig. 2 was changed. The home-made oscillator, the frequency and the power supply were replaced with an HP 4395A Network/Spectrum/Impedance Analyser (Hewlett-Packard) coupled with an HP 43961A impedance test kit and HP 16092A spring clip fixture. This new experimental setup was used to make impedance measurements on the acoustic wave sensor. The values of the equivalent circuit elements of the resonator were calculated internally by the HP 4395A from the measured data.

The piezoelectric quartz crystals were 9 MHz, polished AT-cut HC-6/U with gold electrodes (ICM-International Crystal Manufacturing Co. Inc.).

An ultraviolet–visible spectrophotometer (Shimadzu UV-2100 PC) was also used for cloud point determinations based on the operational definition. Glass cuvettes with 1 cm path were filled with the HPMC solution.

2.3. Experimental procedure

2.3.1. Preparation of gels

Aqueous solutions of 0.5, 1, 2 and 4% (w/w) of HPMC were prepared by adding the appropriate amount of dry polymer to Milli-Q water. After gently stirring for a few hours, the solutions were kept at 4 °C for several days.

2.3.2. Analysis with the acoustic wave sensor

HPMC solutions were heated at a chosen rate from room temperature to near 90 °C and left to cool. The temperature inside the HPMC samples was monitored with a Pt100 sensor previously calibrated. The frequency of oscillation of the quartz crystal in contact with the HPMC solution, along with temperature, was stored at intervals of 5 s in a personal computer using a LabView program, written specifically for this purpose.

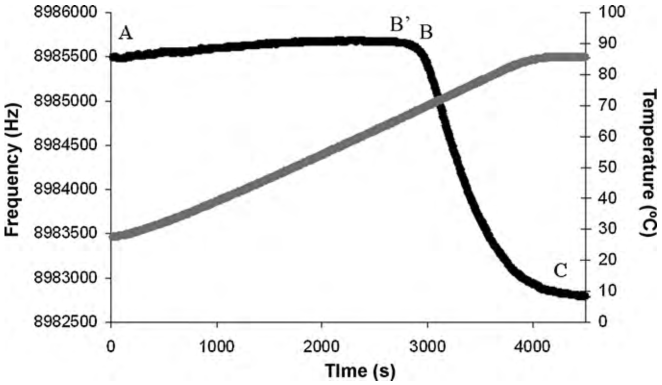

Fig. 3. Series frequency (Hz) for a 9-MHz piezoelectric quartz crystal in contact with 2% (w/w) HMPC.

The measurements taken from the impedance analyser were initially made within a frequency span that extended over the entire region of interest of the sensor, from 8 to 10 MHz. Subsequently, the impedance analyser scanned 801 points around one of the frequencies at zero phase (series frequency), with 100 kHz bandwidth. The instrument was calibrated and test fixture compensated. The equivalent circuit electrical parameters were computed by the instrument.

2.3.3. Cloud point

For cloud point determination, the transmittance was measured at a wavelength of 800 nm (Xu et al., 2006). Initially, readings were taken at 5 °C intervals, which were reduced to 1 °C near the transition point. The samples were transferred to the cuvette very carefully to prevent air bubbles that could lead to false values if trapped inside the gel.

3. Results and discussion

3.1. Using an acoustic wave sensor to follow HPMC solution gelation

Fig. 3 shows the series frequency of the quartz crystal in contact with 2% (w/w) HMPC solution, during a temperature rise (1 °C/min) from room temperature to 87 °C. From this figure it can be seen that, from point A to point B′, the frequency of the crystal slowly increases. Silva et al. (2008) have already shown that random entanglements, the weakening of intermolecular interactions and the loss of hydration water of the polymer result in a slow decrease

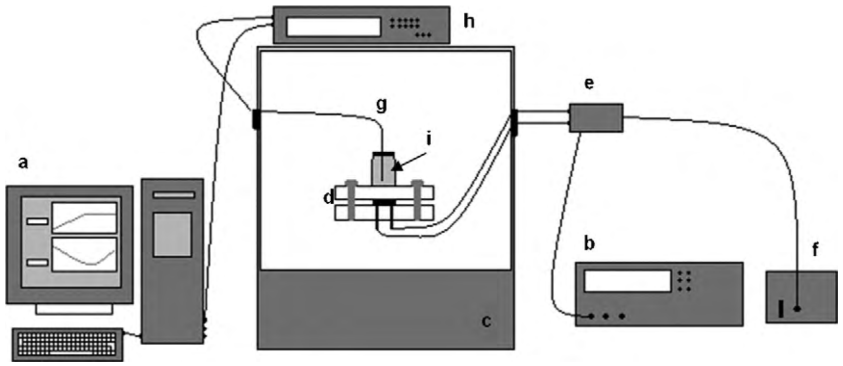

Fig. 2. Experimental setup: (a) personal computer; (b) frequencymeter; (c) thermostatic chamber; (d) Teflon cell with quartz crystal; (e) home-made oscillator; (f) power supply; (g) temperature sensor Pt100; (h) multimeter and (i) HPMC solution (light grey).

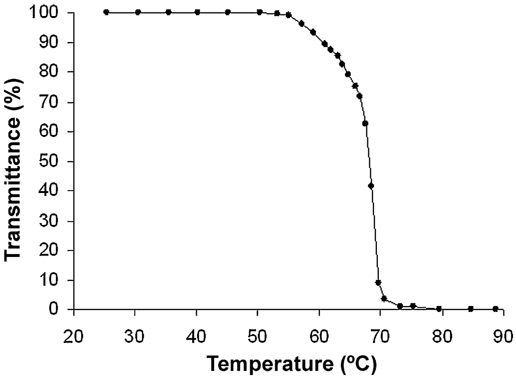

Fig. 4. Transmittance values (λ = 800 nm) found for a 2% (w/w) HPMC solution.

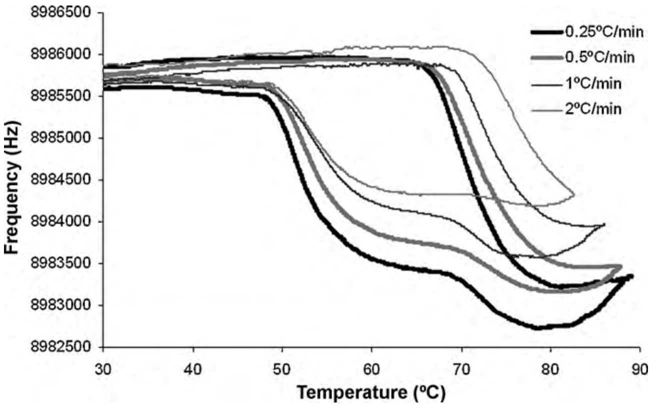

Fig. 5. Hysteresis for a 0.5% (w/w) HPMC solution for different heating rates.

of viscosity in this temperature range. According to the Bruckenstein and Shay equation (Bruckenstein & Shay, 1985), the decrease in viscosity causes an increase in frequency, which is consistent with these observations. From B′, to point C, the increase in the hydrophobic character of the system with increasing temperature starts to cause the formation of aggregates (polymer–polymer associations) and the increase in the viscosity results in a frequency decrease. Point B marks the start of the sharp decrease of the frequency and its value (68.5 °C) was found after drawing tangent lines to the curve. At point B aggregates attain a critical concentration and gelation begins.

The cloud point is often defined as the temperature at which light transmission reaches 50% of its initial value. Its determination must rely on a careful procedure, as values found in the literature are not in agreement. For example, Silva et al. (2008) reported a value of 68 °C for a 2% (w/w) HPMC solution while Xu et al. (2006) reported a value of 70.9 °C for the same HPMC solution.

Transmittance at a wavelength of 800 nm was measured for 2% (w/w) HPMC solution, and the results are presented in Fig. 4. From these the cloud point value was found to occur at 68.2 °C, which is very close to the previously mentioned B point.

It can also be concluded from Fig. 3 that the gelation process continues after point B onwards. Frequency experiences a marked decrease until point C is reached (full gelation). An interval of 17 °C separates the starting of the gelation process (point B) from the point at which the process can be considered complete (point C), which probably explains the large difference in the literature values found for the gelation temperature. For Silva et al. (2008) gelation point for a 2% HPMC solution is 71 °C while for Xu et al. (2006) gelation point for the same HPMC solution is found at 87.82 °C. According to product specifications (Methocel, 2009) for the Methocel K brand, the approximate gelation temperature for a 2% aqueous solution is close to 70 °C.

These differences may be ascribed to the methodology used, the heating rates, but also to the fact that continuous readings were not possible with the methods previously used. In contrast, the frequency of the acoustic wave sensor in contact with the HPMC solution was monitored continuously, and therefore, the very beginning and ending of the gelation process was easily observed.

3.2. Thermoreversible gelation and heating/cooling rates

In order to understand the effect of the heating and cooling rates on the gel thermoreversibility, several heating rates were tested and the frequency of oscillation of the sensor in contact with the HPMC solution was monitored.

Fig. 5 shows the thermoreversibility of a 0.5% (w/w) HPMC solution when heating the oven from room temperature to 90 °C and cooling. Several heating rates, namely 0.25, 0.5, 1 and 2 °C/min were tested while the cooling rate was approximately 0.25 °C/min. The temperature values shown in Fig. 5 were obtained inside the HPMC solution with the temperature sensor PT100. From Fig. 5, it can be seen that for the highest temperature rate, 2 °C/min, the maximum temperature attained inside the HPMC solution was 82.6 °C, which was shown to be insufficient for achieving full gelation, since the frequency was still decreasing at a constant rate when the maximum temperature inside the solution was reached. For the other three heating rates tested, namely 0.25, 0.5 and 1.0 °C/min, Fig. 5 shows that the maximum temperature achieved inside the HPMC solution was 89.1, 87.9 and 86.0 °C, respectively. For all these heating rates, full gelation of the HPMC solution was induced and, in these cases frequency stabilizes at 81.1, 82.8 and 83.2 °C, respectively.

These observations allow to conclude that higher heating rates lead to higher temperatures for initiation of the gelation process, resulting from the convolution of gelation kinetics and heating rate, with values 66.6, 67.3, 69.3 and 70.4 °C with heating rates of 0.25, 0.5, 1 and 2 °C/min, respectively. This is an important issue, which shows once again the difficulty in obtaining data matching the gelation temperature found by other authors. Since a heating rate of 0.25 °C/min leads to very long experiments, approximately 9 h for the heating step, heating rates of 0.5 or 1 °C/min were chosen for all subsequent experiments. None of the measurements were conducted at equilibrium, which is also true for those found in the literature. In an attempt to obtain the true equilibrium gelation temperature, which should be obtained isothermally, i.e. with a very low heating rate (Barba et al., 2009b), values determined for the onset of gelation were plotted versus the heating rate. The gelation temperature extrapolated for a 0 °C/min heating rate was 66.4 °C.

The cooling rate for all the experiments in Fig. 5 was approximately 0.25 °C/min. According to Li et al. (2001), if the sample is allowed to equilibrate for some time before cooling starts, the gel should be more difficult to dissociate in the cooling process because of the more perfect network formed. Nevertheless, thermal recovery in the cooling process does not follow the same path as that of the heating process, nor frequency is changing with a constant velocity during the cooling step, as observed in Fig. 5. This irregular behaviour can be explained by the existence of some different areas inside the gel, with full dissociation of aggregates coexisting with weak connections that have not been completely dissociated (Li et al., 2001) when reaching B temperature. Thus, a higher gelation temperature is found on heating, and a lower gelation temperature on cooling.

It can also be concluded from the discussion in Fig. 5 that the degree of thermoreversibility depends on the heating and cooling rates, and a careful choice should be done for both rates.

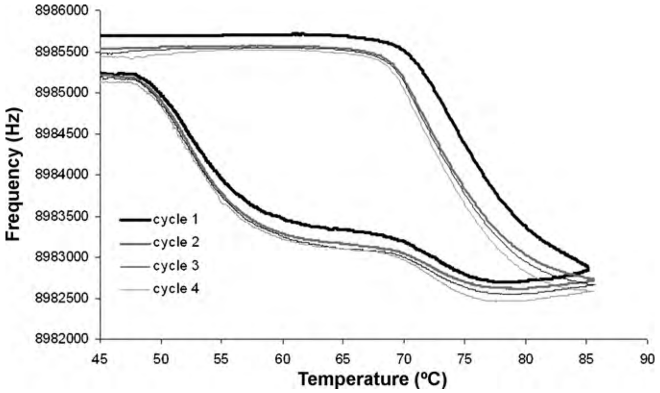

Fig. 6. Four consecutive thermal cycles: heating (1 °C/min) and cooling (0.25 °C/min) for a 1% (w/w) HPMC solution.

3.3. *Heating/cooling cycles*

Fig. 6 shows four consecutive heating (1 °C/min) and cooling (0.25 °C/min) cycles for a 1% (w/w) HPMC solution maintaining the heating and cooling rates. As can be seen in Fig. 6, the temperature at which the gelation process begins decreases with the increase in the number of cycles. The highest difference occurs between the first and second cycles, and the gelation temperature is 69.6, 65.7, 65.4 and 65.3 °C for cycles 1, 2, 3 and 4, respectively. As mentioned in the apparatus section, a septum was used to close the cell to prevent water evaporation from the HPMC solution. Nevertheless, the possibility that this decrease in gelation temperature is due to some water evaporation cannot be completely ruled out, and a decrease in frequency with the cycle number is consistent with the increase in the concentration of the solution.

Further experiments are needed to conclude whether temperature changes may lead to some permanent changes on the physical properties of the HPMC solution.

3.4. *Concentration of HPMC water solutions*

Table 1 shows the temperatures at which gelation begins, for several HPMC solutions, namely 0.5, 1, 2 and 4% (w/w), with an heating rate of 1 °C/min. Except for the 0.5% (w/w) HPMC solution, the beginning of gelation takes place at lower temperatures for the more concentrated solution, which is in the line of results from other authors (Ford, 1999).

3.5. *The equivalent electrical parameters of the acoustic wave sensor in contact with the HPMC solution*

Since frequency changes do not fully characterize the sensor, the impedance of the quartz crystal in contact with the HPMC solution was monitored and the equivalent electrical parameters computed. Therefore, besides the series frequency (F) already shown, the most relevant parameters found for characterization of the HPMC solutions, the resistance (R_m) and the inductance (L_m) of the equivalent electrical circuit, will now be discussed.

Table 1
Temperatures at which gelation begins, for HPMC aqueous solutions, at a heating rate of 1 °C/min.

% (w/w) HPMC	$T_{\text{gelation begins}}$ (°C)
0.5	69.3
1.0	69.5
2.0	68.5
4.0	68.3

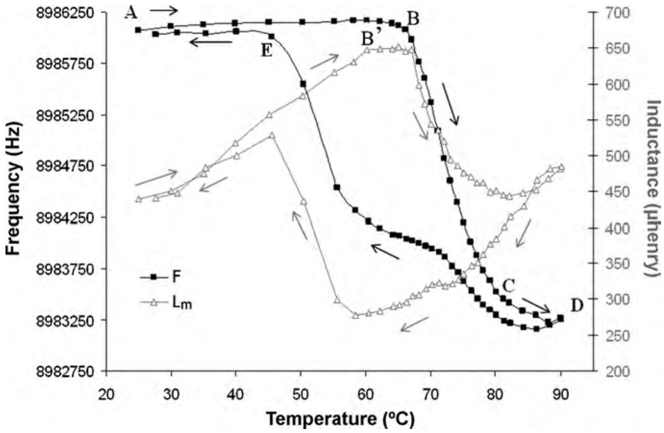

Fig. 7. Series frequency (f/Hz) and inductance (L_m/µhenry) for a 2% (w/w) HPMC aqueous solution, during a thermocycle (heating rate 0.5 °C/min and cooling rate 0.25 °C/min).

Fig. 7 shows F and L_m and Fig. 8 shows F and R_m changing during a thermo cycle for a 2% (w/w) HPMC solution. The heating rate was 0.5 °C/min and cooling rate was 0.25 °C/min.

Frequency starts to decrease and L_m stops to increase at 60.2 °C (B′). Afterwards, while frequency measurements start to decrease, both L_m and R_m display a small plateau, between B′ and B or B″. The gelation temperature (B point) occurs at 66.7 °C when frequency experiences a drastic decrease, very close to the point where L_m starts to decrease and R_m to increase.

A possible interpretation for the F, L_m and R_m behaviour displayed in Figs. 7 and 8 could be envisaged taking into account the latest work of Bajwa et al. (2009), on molecular and mechanical properties of HPMC Methocel E4M solutions during sol–gel transitions (in accordance with the mechanism suggested by Silva et al. (2008) for HPMC). Their report is consistent with the observation of four distinct phases during the heating cycle. From point A (room temperature) to point B′ (60.2 °C) it occurs the disruption of the cellulosic “bundles”, with an increase in the polymer chain mobility and the weakening of polymer–water hydrogen bonding. From point B′ (60.2 °C) to point B (66.7 °C) occurs the formation of a tenuous network of swollen clusters that resulted from “unbundling” phenomena (increase in volume). From point B (66.7 °C) to point C (80.1 °C) there is the formation of a coherent elastic gel structure, and finally from point C (80.1 °C) to point D (90 °C) we are in pres-

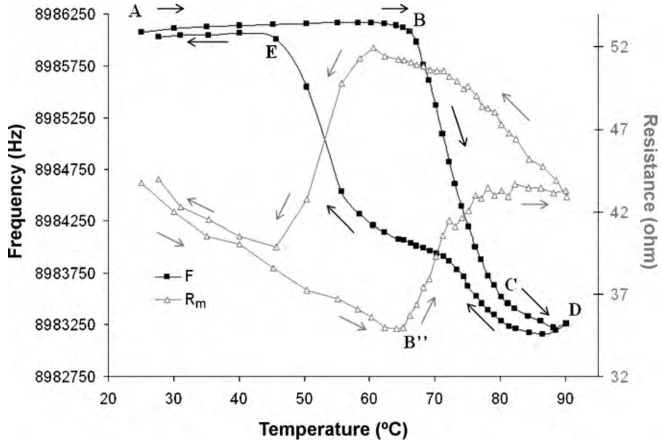

Fig. 8. Series frequency (f/Hz) and resistance (R_m/ohm) for a 2% (w/w) HPMC aqueous solution, during a thermocycle (heating rate 0.5 °C/min and cooling rate 0.25 °C/min).

ence of an elastic gel which exhibit little frequency and resistance dependence with temperature.

A direct comparison between the temperatures at B′, B, C and D found in this work with the results of Bajwa et al. (2009) is however not possible, since different types of Methocel (K15 M and E4 M, respectively) were used. The type of HPMC used in this work has a larger number of hydroxypropyl substitutions than the one used by Bajwa et al. (2009) and a higher gelation temperature is expected, and confirmed by the observations.

During the cooling cycle, frequency increases till its maximum value, while L_m decreases and R_m increases till near the gelation point, after which the changing of these parameters are reversed. Frequency attains a constant value at E point (40.5 °C) while at this same temperature L_m starts to decrease and R_m to increase.

It should be noted that both the evolution of inductance and resistance values allows to observe a further aspect of the system that is hardly, or not at all, detected in the frequency readings, and is also mostly absent in previous thermorheological work. In the latter, the system approximately follows, upon cooling, the reverse behaviour found on heating, in spite of some delay. If we once again inspect Fig. 7, it is seen that the frequency mostly decreases from point B to D (except in the proximity of D) and that, when temperature starts to decrease, it rapidly starts to increase, thus reversing the trend found upon heating. In what concerns the inductance readings it is seen that they decrease from point B onwards and approximately stabilize (or slightly increase) close to 80 °C. When the temperature is lowered, it continues to decrease and increases only for values of the temperature lower than 60 °C. In turn, the resistance values increase after point B″, stabilize (or just slightly decrease) close to 80 °C, and then increase again when the temperature is lowered. Both inductance and resistance measurements show that as long as temperatures are higher than the gelation point, the trend of increasing or decreasing of these electrical parameters pursue, irrespectively of the sign of temperature variation. This independence of the sign of temperature variation is consistent with the previous statements that these parameters are really changing with the system and are not seen on the frequency or rheological measurements. Besides, this highlights the fact that gelation is a complex mechanism, involving more than one process, and the increased hydrophobicity of the polymer above the gelation temperature promotes its evolution, irrespective of the external imposition of a rising or decreasing temperature.

It should also be noted that, when attaining high temperatures (>80 °C) in the system, frequency, inductance and resistance display a common behaviour: they stabilize and slightly reverse the previous ascending or descending trend. This suggests that high temperatures tend to disrupt the gel (gel → sol transition), as observed in other systems (Song, Lee, Ahn, Kim, & Kimi, 2000). This behaviour is readily reversed upon cooling, unlike what happens to the dominant trends for inductance and resistance.

4. Conclusions

The active acoustic methodology, which uses an oscillator and is relatively inexpensive, allows detecting the gelation point during the heating cycle. However, its detection during cooling is not so straightforward. The measurement of the equivalent electric parameters, which demands a more expensive apparatus, confirms the value found for the gelation point, which is now easier to point out, and also allows its detection during the cooling cycle. Besides, the region between B′ and B, where frequency changes at a very slow rate, appears now as a plateau in which concerns to inductance, which helps to interpret this region as one in which the number of aggregates increases up to a critical concentration, but without a significant change at the "molecular level". B marks a major change, with gel formation. This behaviour has already been described for PEO–PPO–PEO triblock copolymer (Alexandridis, Holzwarth, & Hatton, 1994) by employing a dye solubilisation method.

The present work has shown that the study of HPMC aqueous solutions using a piezoelectric quartz crystal allows to obtain a picture of the occurring changes that vastly complements that obtained by traditional rheological methods.

Acknowledgments

This project was financed by the FCT, POCTI, FEDER and CESAM.

References

Alexandridis, P., Holzwarth, J. F., & Hatton, T. A. (1994). Micellization of poly(ethylene oxide)poly(propylene oxide)–poly(ethylene oxide) triblock copolymers in aqueous solutions: Thermodynamics of copolymer association. *Macromolecules*, *27*, 2414–2425.

Bajwa, G. S., Sammon, C., Timmins, P., & Melia, C. D. (2009). Molecular and mechanical properties of hydroxypropyl methylcellulose solutions during the sol:gel transition. *Polymer*, *50*, 4571–4576.

Bandey, H. L., Martin, S. J., & Cernosek, R. W. (1999). Modeling the responses of thickness-shear mode resonators under various loading conditions. *Analytical Chemistry*, *71*, 2205–2214.

Barba, A. A., d'Amore, M., Cascone, S., Chirico, S., Lamberti, G., & Titomanlio, G. (2009a). On the behavior of HPMC/theophylline matrices for controlled drug delivery. *Journal of Pharmaceutical Sciences*, *98*, 4100–4110.

Barba, A. A., d'Amore, M., Grassi, M., Chirico, S., Lamberti, G., & Titomanlio, G. (2009b). Investigation of Pluronic© F127-water solutions phase transitions by DSC and dielectric spectroscopy. *Journal of Applied Polymer Science*, *114*, 688–695.

Bund, A., Chmiel, H., & Schwitzgebel, G. (1999). Determination of the complex shear modulus of polymer solutions with piezoelectric resonators. *Physical Chemistry Chemical Physics*, *1*, 3933–3938.

Burdock, G. A. (2007). Safety assessment of hydroxypropyl methylcellulose as a food ingredient. *Food and Chemical Toxicology*, *45*, 2341–2351.

Bruckenstein, S., & Shay, M. (1985). Experimental aspects of use of the quartz crystal microbalance in solution. *Electrochimica Acta*, *30*, 1295–1300.

Conti, S., Maggi, L., Segale, L., Machiste, E. O., Conte, U., Grenier, P., & Vergnault, G. (2007). Matrices containing NaCMC and HPMC. 1 Dissolution performance characterization. *International Journal of Pharmaceutics*, *333*, 136–142.

Chirico, S., Dalmoro, A., Lamberti, G., Russo, G., & Titomanlio, G. (2007). Analysis and modeling of swelling and erosion behavior for pure HPMC tablet. *Journal of Controlled Release*, *122*, 181–188.

Desbrières, J., Hirrien, M., & Rinaudo, M. (1998). A calorimetric study of methylcellulose gelation. *Carbohydrate Polymers*, *37*, 145–152.

Desbrières, J., Hirrien, M., & Ross-Murphy, S. B. (2000). Thermogelation of methylcellulose: Rheological considerations. *Polymer*, *41*, 2451–2461.

Ford, J. L. (1999). Thermal analysis of hydroxypropylmethylcellulose and methylcellulose: Powders, gels and matrix tablets. *International Journal of Pharmacology*, *179*, 209–228.

Hardy, I. J., Windberg-Baarup, A., Neri, C., Byway, P. V., Booth, S. W., & Fitzpatrick, S. (2007). Modulation of drug release kinetics from hydroxypropyl methyl cellulose matrix tablets using polyvinyl pyrrolidone. *International Journal of Pharmacology*, *337*, 246–253.

Holt, R. C., & Gouws, G. J. (2004). The use of bulk acoustic wave devices as probes of material properties. *Current Applied Physics*, *4*, 296–299.

Holt, R. C., Gouws, G. J., & Zhen, J. Z. (2006). Measurement of polymer shear modulus using thickness shear acoustic waves. *Current Applyed Physics*, *6*, 334–339.

Hussain, S., Keary, C., & Craig, D. Q. M. (2002). A thermorheological investigation into the gelation and phase separation of hydroxypropyl methylcellulose aqueous systems. *Polymer*, *43*, 5623–5628.

Kita, R., Kaku, T., Kubota, K., & Dobashi, T. (1999). Pinning of phase separation of aqueous solution of hydroxypropylmethylcellulose by gelation. *Physical Letters A*, *259*, 302–307.

Kobayashi, K., Huang, C., & Lodge, T. P. (1999). Thermoreversible gelation of aqueous methylcellulose solutions. *Macromolecules*, *32*, 7070–7077.

Kudryashov, E. D., Hunt, N. T., Arikainen, E. O., & Buckin, V. A. (2001). Monitoring of acidified milk gel formation by ultrasonic shear wave measurements: High-frequency viscoelastic moduli of milk and acidified milk gel. *Journal of Dairy Science*, *84*, 375–388.

Li, L. (2002). Thermal gelation of methylcellulose in water: Scalling and thermoreversibility. *Macromolecules*, *35*, 5990–5998.

Li, L., Thangamathesvaran, P. M., Yue, C. Y., Tam, K. C., Hu, X., & Lam, Y. C. (2001). Gel network structure of methylcellulose in water. *Langmuir*, *17*, 8062–8068.

Liu, S. Q., Joshi, S. C., Lam, Y. C., & Tam, K. C. (2008). Thermoreversible gelation of hydroxypropylmethylcellulose in simulated body fluids. *Carbohydrate Polymers*, *72*, 133–143.

Lucklum, R., & Hauptmann, P. (1997). Determination of polymer shear modulus with quartz crystal resonator. *Faraday Discussions*, *107*, 123–140.

Martin, S. J., Granstaff, V. E., & Frye, G. C. (1991). Characterization of a quartz crystal microbalance with simultaneous mass and liquid loading. *Analytical Chemistry*, *63*, 2272–2281.

Methocel (2009) in http://www.methocel.com (at 16/09/2009).

Nilsson, S. (1995). Interactions between water-soluble cellulose derivatives and surfactants.1. The HPMC/SDS/water system. *Macromolecules*, *28*, 7837–7844.

Nomura, T., & Minemura, A. (1980). Behavior of a piezoelectric quartz crystal in an aqueous solution and the application to the determination of minute amount of cyanide. *Nippon Kagaku Kaishi*, *10*, 1621–1625.

Nomura, T., & Okuhara, M. (1982). Frequency shifts of piezoelectric quartz crystals immersed in organic liquids. *Analytical Chimica Acta*, *142*, 281–284.

Reddy, S. M., Jones, J. P., & Lewis, T. J. (1997). Use of combined shear and pressure acoustic waves to study interfacial and bulk viscoelastic effects in aqueous polymeric gels and the influence of electrode potentials. *Faraday Discussions*, *107*, 177–196.

Ridel, A., Evertsson, H., Nilsson, S., & Sundelöf, L.-O. (1999). Amphiphilic association of ibuprofen and two nonionic cellulose derivatives in aqueous solution. *Journal of Pharmaceutical Sciences*, *88*, 1175–1181.

Sabot, A., & Krause, S. (2002). Simultaneous quartz crystal microbalance impedance and electrochemical impedance measurements: Investigation into the degradation of thin polymer films. *Analytical Chemistry*, *74*, 3304–3311.

Sarkar, N. (1995). Kinetics of thermal gelation of methylcellulose and hydroxypropylmethylcellulose in aqueous solutions. *Carbohydrate Polymers*, *26*, 195–203.

Sarkar, N., & Walker, L. C. (1995). Hydration–dehydration properties of methylcellulose and hydroxypropylmethylcellulose. *Carbohydrate Polymers*, *27*, 177–185.

Siepmann, J., & Peppas, N. A. (2001). Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Advance Drug Delivery Review*, *48*, 139–157.

Silva, S. M. C., Pinto, F. V., Antunes, F. E., Miguel, M. G., Sousa, J. J. S., & Pais, A. A. C. C. (2008). Aggregation and gelation in hydroxypropylmethyl cellulose aqueous solutions. *Journal of Colloid and Interface Science*, *327*, 333–340.

Song, M. J., Lee, D. S., Ahn, J. H., Kim, D. J., & Kimi, S. C. (2000). Dielectric behavior during sol–gel transition of PEO–PPO–PEO triblock copolymer aqueous solution. *Polymer Bulletin*, *43*, 497–504.

Xu, X. M., Song, Y. M., Ping, Q. N., Wang, Y., & Liu, X. Y. (2006). Effect of ionic strength on the temperature-dependent behavior of hydroxypropyl methylcellulose solution and matrix tablet. *Journal of Applied Polymer Science*, *102*, 4066–4074.

Weng, L., Zhang, L., Ruan, D., Shi, L., & Xu, J. (2004). Thermal gelation of cellulose in a NaOH/thiourea aqueous solution. *Langmuir*, *20*, 2086–2093.