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Following HPMC gelation with a piezoelectric quartz crystal

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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-

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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, $M_\mathrm{w} = 4.3 \times 10^5$ 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