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Characterisation of water behaviour in cellulose ether polymers using low frequency dielectric spectroscopy

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Abstract

The behaviour of water in hydroxypropylmethylcellulose (HPMC) K100LV, K4M, K15M, K100M, E4M, F4M and HPC polymers was characterised using low frequency dielectric spectroscopy (LFDS). Dielectric responses of 25% (w/w) HPMC K15M gels and deionised water were found to be similar at +22 and 0 °C. However, at −30 °C, a dielectric response typical of a solid was apparent. The melting of frozen water within gels was detected as increases in the magnitude of the dielectric response with increase in temperature. More than one phase transition was visible in the majority of gels studied which may be related to the presence of different states of water melting at different temperatures. In addition to polymer concentration, both polymer molecular weight and substitution level influenced the nature of the transitions. The magnitude of the dielectric response was increased in all HPMC gel systems in comparison to the response seen in deionised water. Drug addition affected the transitions occurring during the melting of ice in the gels. This may be related to the presence of ionic species in the systems. LFDS studies on cellulose ether gels have provided some interesting evidence for the existence of more than one state of water within such gel systems. The results are in good agreement with thermal analysis findings in similar gel systems.

Keywords: Hydroxypropylmethylcellulose; Cellulose ether; Low frequency dielectric spectroscopy; Water; Phase transitions

1. Introduction

Cellulose ethers have been commonly used in hydrophilic matrix controlled release drug delivery systems. When the device comes into contact with an aqueous medium, a gelatinous layer forms at the tablet surface which provides a method of controlling drug release (Melia, 1991). The structure across this barrier layer is complex and it has been shown that the water mobility across the gel

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layer is not uniform (Rajabi-Siahboomi et al., 1996). Detailed analysis of the types of water which exist within the gel layer are fundamental to the understanding of the mechanism of drug release and also the factors that may affect it.

Previous studies on hydroxypropylmethylcellulose (HPMC) polymer gels using differential scanning calorimetry (McCrystal et al., 1997a) have shown that distinctive thermal events were apparent on the DSC scans of the gels. These events were present on the low temperature side of the main melting endotherm for the melting of free water and have been related to the presence of more than one state of water bound to varying extents within the polymer gel system. The nature of these distinctive thermal events was reported to be dependent on polymer molecular weight, polymer substitution type, polymer concentration and drug addition (McCrystal et al., 1996, 1997b). In the case of HPMC K15M gels, these events were further influenced by gel storage time and cooling and heating rates employed during scanning (McCrystal et al., 1997b).

Low frequency dielectric spectroscopy (LFDS) involves measurement of dielectric behaviour over the frequency range of 10^{-4} to 10^{7} Hz and in simple terms it measures the electrical properties of a material from which information related to the structure and behaviour of the material may be elucidated (Craig, 1992). A dielectric material is a material which contains dipoles and the majority of pharmaceutical systems may thus be classified as dielectrics. When an alternating field is applied to such a material the dipoles will try to re-orientate themselves in the direction of the field in an attempt to maintain overall neutrality. On application of an alternating field, a phase lag develops between the field and the polarisation as the dipoles attempt to relax at the same rate as the changes in field direction. Thus the response of the sample may be described by two parameters; the magnitude of the response and the phase relationship between the stimulus (field) and the response. The susceptibility becomes vectorial (χ^*) and is hence more conveniently described as:

$$\chi^* = \chi' - i\chi'', \tag{1}$$

where χ' and χ'' are the real (energy storage) and imaginary (energy loss) components of the susceptibility, respectively and i is $\sqrt{-1}$. These components may be measured in terms of real and imaginary permittivities (permittivity is a measure of the ease with which a sample polarises and is an intrinsic property of a particular sample).

In practice, the response is measured in terms of the capacitance (C) and dielectric loss (G/ω) where G is the conductance and ω is the frequency. Capacitance is considered to be the real component and dielectric loss as the imaginary component of the response. These may be related to the real and imaginary permittivities by:

$$C(\omega) = \frac{\varepsilon_0 A}{d}(\chi'(\omega) + \varepsilon_\varphi), \tag{2}$$

$$\frac{G(\omega)}{\omega} = \frac{\varepsilon_0 A \chi''(\omega)}{d}, \tag{3}$$

where A and d are the area and separation distance of the electrodes, respectively, ε_0 is the permittivity of free space and ε_φ is the permittivity at infinite frequencies.

The values of capacitance and dielectric loss are measured over a range of frequencies and examination of both their absolute magnitudes and also the relationship between the two parameters may lead to information regarding the structure of the sample under study. More detail about the theory of dielectric spectroscopy may be found in the texts of Hill and Jonsher (1983) and Craig (1995). Gel systems have previously been characterised using LFDS (Binns et al., 1992; Craig et al., 1992, 1994) and the behaviour of water in polymeric systems has previously been characterised by analysis of the dielectric response (Pathmanathan and Johari, 1994; Kyritsis et al., 1995).

In this paper, the dielectric properties of cellulose ether gels were investigated using LFDS and the results were related to previous characterisation carried out using thermal analysis. The dielectric response of the gels over a range of frequencies (10^{-2} to 10^{+7} Hz) at constant temperature and also a range of temperatures (-30 to $+20$ °C) at frequencies of 1 and 100 Hz were measured. The influences of polymer concentration, molecular weight, substitution levels and addition of the drugs propranolol hydrochloride (P.H.) and diclofenac sodium (DIC Na) on their

characteristic dielectric responses were investigated.

2. Materials and methods

2.1. Materials

Methocel (HPMC) cellulose ethers HPMC K100LV, HPMC K4M, HPMC K15M, HPMC K100M, HPMC E4M, HPMC F4M and methylcellulose (MC) A4M (Supplied by Colorcon Ltd, Dartford, UK) were used. Hydroxypropylcellulose (HPC) was obtained from Hercules Limited, Aqualon Division, Salford, UK.

P.H. and DIC Na were obtained from Becpharm, Harlow, Essex, England and Profarmaco, Milan, Italy, respectively.

2.2. Methods

2.2.1. Gel preparation

Cellulose ether gels (2–25% w/w) (sample size 20 g) were prepared by heating the full quantity of distilled water to ~ 80 °C and adding in two aliquots to the previously weighed cellulose ether powder in a mortar and pestle. The mixture was triturated vigorously to ensure thorough wetting. Gels containing P.H. (50 mM) or DIC Na (50 mM) were prepared by dissolving the drugs in distilled water by mixing with the aid of gentle heat on a hot plate stirrer prior to gel preparation. Both drugs were fully soluble in warm water at the chosen concentration. Gels were transferred to pyrex storage vessels which were sealed and stored at 4–6 °C for 24 h before use.

2.2.2. Dielectric spectroscopy analysis

A Novocontrol Broadband Dielectric Converter BDC (Hundsangen, Germany) with an attached QUATRO temperature controller was employed. Gel samples were transferred to a round plate electrode dielectric cell (diameter (d) = 20 mm; thickness = 0.5 mm). The Novocontrol BDC was used to apply an alternating voltage of 0.5 V across the sample. Dielectric spectra for HPMC K15M gels were obtained over frequency sweeps from 10^{-2} to 10^{7} Hz at a constant temperature of 22 °C. From this work, a frequency of 1 Hz was chosen and gels were subjected to temperature sweeps from -30 to $+20$ °C at a scanning rate of $+1$ °C min^{-1}, and their dielectric responses were recorded. In addition, their dielectric response at constant temperatures of -30, 0 or $+22$ °C were recorded over a frequency range of 10^{-2} to 10^{7} Hz. Each dielectric response at a particular temperature or frequency represents an average of at least two measurements with each set of measurements being repeated at least twice.

3. Results and discussion

3.1. Dielectric response of HPMC K15M gels

3.1.1. Effect of temperature on the nature of the dielectric response

Fig. 1 shows the dielectric response of HPMC K15M (25% w/w) gels and deionised water over a frequency range of 10^{-2} to 10^{+7} Hz at a constant temperature of 22 °C. The overall dielectric response of the HPMC K15M gels follows the same pattern as that of the deionised water. However, an increase in magnitude of both the capacitance ($\log Cp'$) and dielectric loss ($\log Cp''$) values occurs in the presence of HPMC K15M. This may be due to the presence of the polymer or indeed due to the effect of ionic species such as Na^{+} and Cl^{-} in the gel systems. At 0 °C, the dielectric response shows a quite similar pattern to that observed at 22 °C. However, deionised water and gel samples scanned at -30 °C show very different dielectric behaviour compared to the response at higher temperatures (Fig. 2). The capacitance of deionised water decreased from -3.5 ($\log F$) at 22 °C to -8.75 ($\log F$) at -30 °C. Similarly, the capacitance of 25% (w/w) HPMC K15M gels decreased from -3.5 ($\log F$) at 22 °C to -6 ($\log F$) at -30 °C approximately. The decrease in magnitude of the dielectric response, which occurs with a decrease in temperature, is related to the reduction in mobility of dipoles in the system as the sample freezes. At 22 °C, the system is liquid and water and other ionic species possess kinetic energy and are mobile. Dipoles within the system can easily respond to an alternating cur-

rent and the dielectric response is therefore large in magnitude. With a reduction in temperature, the kinetic energy of the dipoles is correspondingly reduced until freezing occurs and thus a dielectric response typical of a solid is apparent. In essence, at −30 °C, water is frozen and the

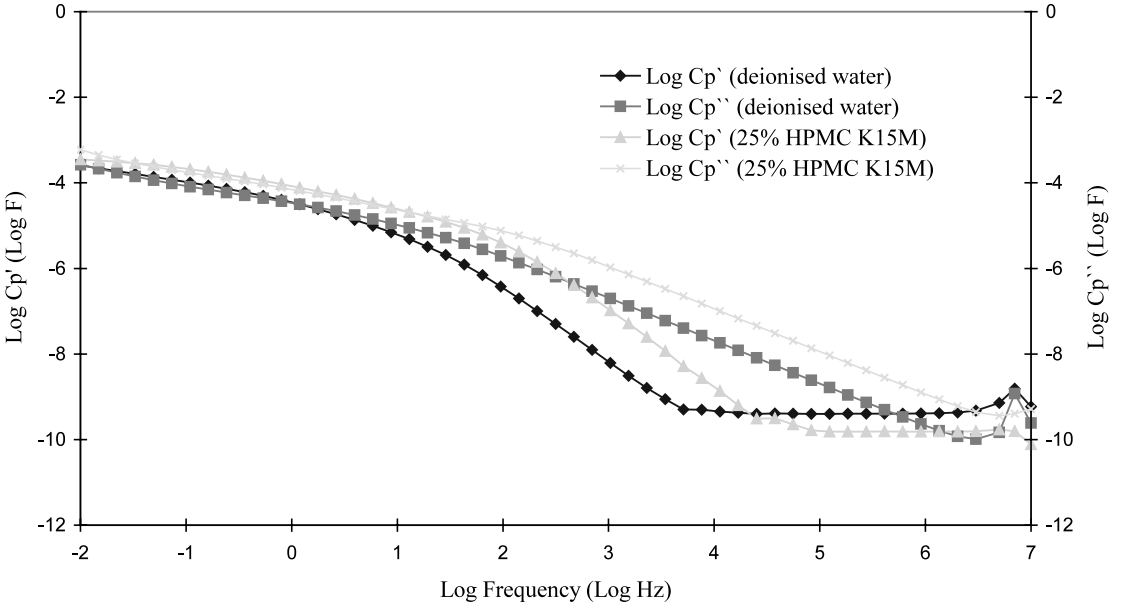

Fig. 1. Log capacitance (log Cp′) (log *F*) and log dielectric loss (log Cp″) (log *F*) against log frequency (log Hz) for deionised water and 25% (w/w) HPMC K15M gels at 22 °C.

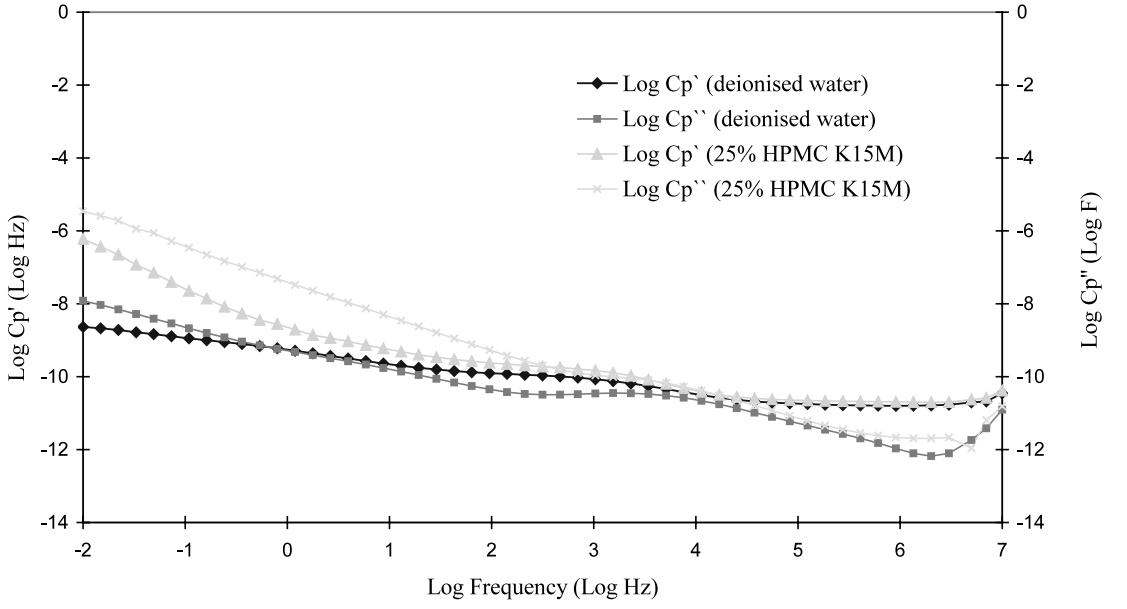

Fig. 2. Log capacitance (log Cp′) (log *F*) and log dielectric loss (log Cp″) against log frequency (log Hz) for deionised water and 25% (w/w) HPMC K15M gels at −30 °C.

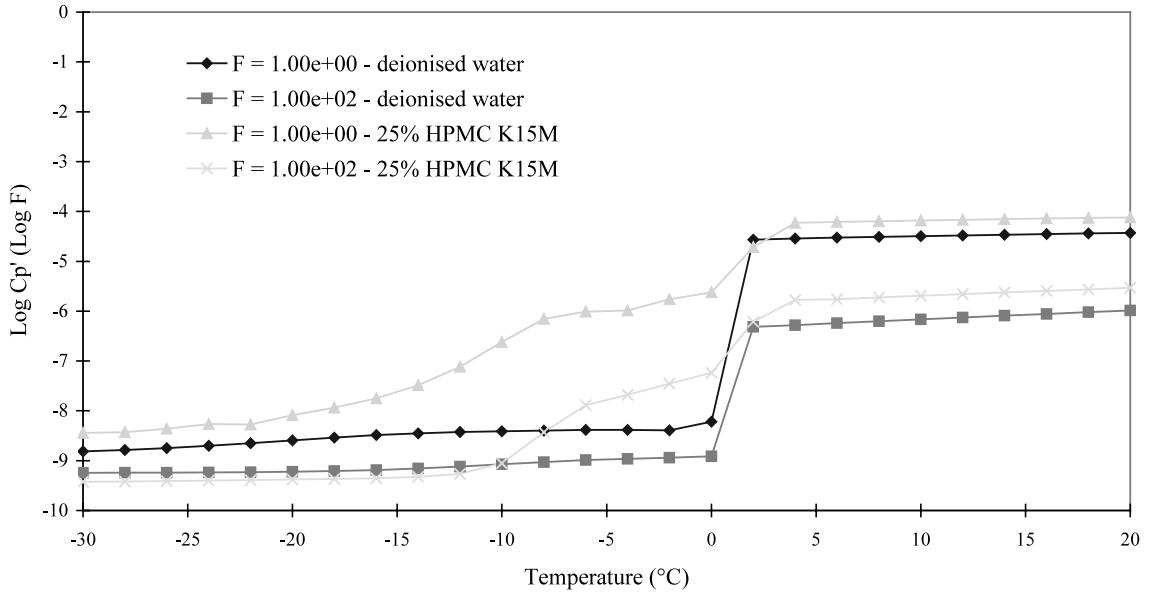

Fig. 3. Log capacitance (log Cp′) (log *F*) against temperature (°C) for 25% (w/w) HPMC K15M gels and deionised water at frequencies of 1 and 100 Hz.

response of the dipoles are typical of those recorded for solids (Craig and Newton, 1993).

The dielectric response of 25% (w/w) HPMC K15M gel samples and that of deionised water were recorded as the temperature of the samples was varied from -30 to $+20$ °C at frequencies of 1 and 100 Hz. The capacitance of the samples are shown in Fig. 3 and is characterised by a sharp increase at the melting point of ice (0 °C). Fig. 3 shows that deionised water showed no change in capacitance over a temperature range of -30 to 0 °C. However, at about 0 °C, a sudden increase in capacitance from -9 to -6.5 at 100 Hz, an increase in capacitance in the order of 1.5, was observed. In the presence of 25% (w/w) HPMC K15M, the dielectric response of the system is different to that observed for deionised water. Fig. 3 shows that at 100 Hz, the value of log Cp′ increases from -9.5 to -6 (log *F*), which is quite similar in magnitude to the increase for deionised water. However, the increase in capacitance begins at about -12 °C and continues to $+4$ °C. This may be related to a depression in the melting point of ice which appears to occur at about -22 and -12 °C in the presence of HPMC K15M at frequencies of 1 and 100 Hz, respectively. Similar trends are observed from the log Cp″ data (not shown). As well as the melting of free water, a number of other processes seem to be occurring as indicated by the shape of the dielectric response curves. These data are in agreement with the findings by DSC (McCrystal et al., 1997a) which have identified more than one event occurring during the melting of ice in HPMC K15M gels of a similar concentration. It is hypothesised that these events may be indicative of the presence of more than one state of water in HPMC K15M gels. Similar pre-endothermic events have also been attributed to overlapping ice melting (first order) and glass transition (second order) phase transitions in maltose and maltodextrins (Roos and Karel, 1991). Ratto et al. (1995) have attributed pre-endothermic events present in water/chitosan systems as being due to cold crystallization. This occurs in systems where only non-freezing and freezing bound water are present. Upon heating, some of the non-freezing water becomes mobile, comes into contact with

solid freezing bound water and forms ice. A crystallization exotherm is subsequently visible.

3.1.2. Effect of HPMC K15M concentration on the dielectric response

The effect of HPMC K15M concentration on the behaviour of water in gel systems has previously been characterised using thermal methods which showed that events occurring on the leading edge of the main endotherm for the melting of free water in HPMC K15M gel systems are polymer concentration dependent. Such events, attributed to the presence of loosely bound water, are present in 20% (w/w) gels but are absent in 10% (w/w) gels (McCrystal et al., 1997a). Figs. 4 and 5 show the dielectric response of deionised water and HPMC K15M (2–25% w/w) gels scanned at 1 Hz. The dielectric response of the gels clearly changes with increase in polymer concentration. Fig. 4 shows that a transition at approximately -8.5 °C becomes more pronounced with increase in polymer concentration. Such a response is also visible in the dielectric loss response at 1 Hz (Fig. 5). Such transitions may be related to events seen on the leading edge of the main endotherm in DSC data in HPMC K15M gels of greater than 15% (w/w) concentration. These are in agreement with DSC studies in showing that more than one type of water exists in HPMC K15M polymer gels. A linear relationship exists between log Cp″ and polymer concentration (Fig. 6). This may suggest that the increase in dielectric response (log Cp″) may be due to the ionic species in the gel samples.

3.2. Effect of polymer molecular weight on the dielectric response of cellulose ether gels

The dielectric spectra of HPMC K-series polymers of similar substitution levels but with increasing molecular weight at a frequency of 1 Hz are shown in Figs. 7 and 8. Both the capacitance and dielectric loss of the gel samples studied indicate that, in addition to the melting of free water, other processes seem to be occurring. This is similar to those previously seen in HPMC K15M gels which may indicate the presence of different states of water. The dielectric response of the gels at these frequencies over a temperature range of -30 to $+20$ °C seems to vary with polymer molecular weight. The temperature at which melt-

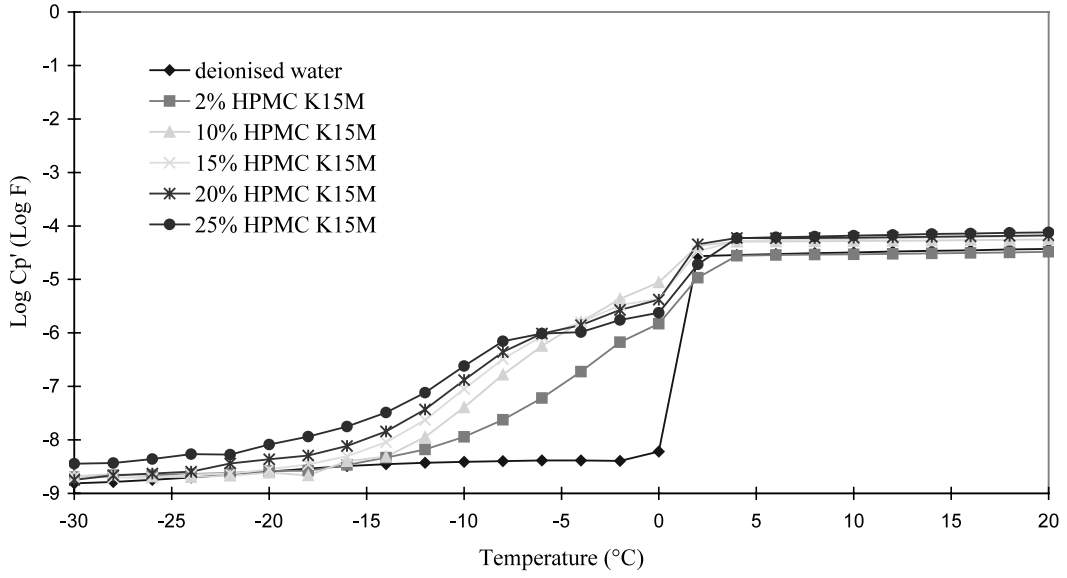

Fig. 4. Log capacitance (log Cp′) (log *F*) against temperature (°C) for 2–25% (w/w) HPMC K15M gels and deionised water at a frequency of 1 Hz.

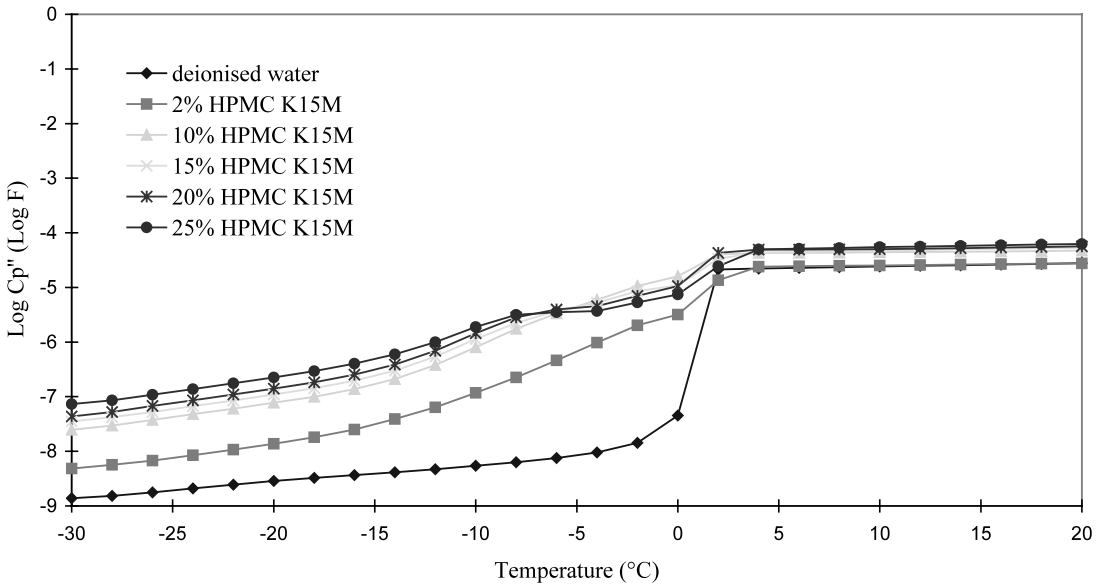

Fig. 5. Log dielectric loss (log Cp″) (log *F*) against temperature (°C) for 2–25% (w/w) HPMC K15M gels and deionised water at a frequency of 1 Hz.

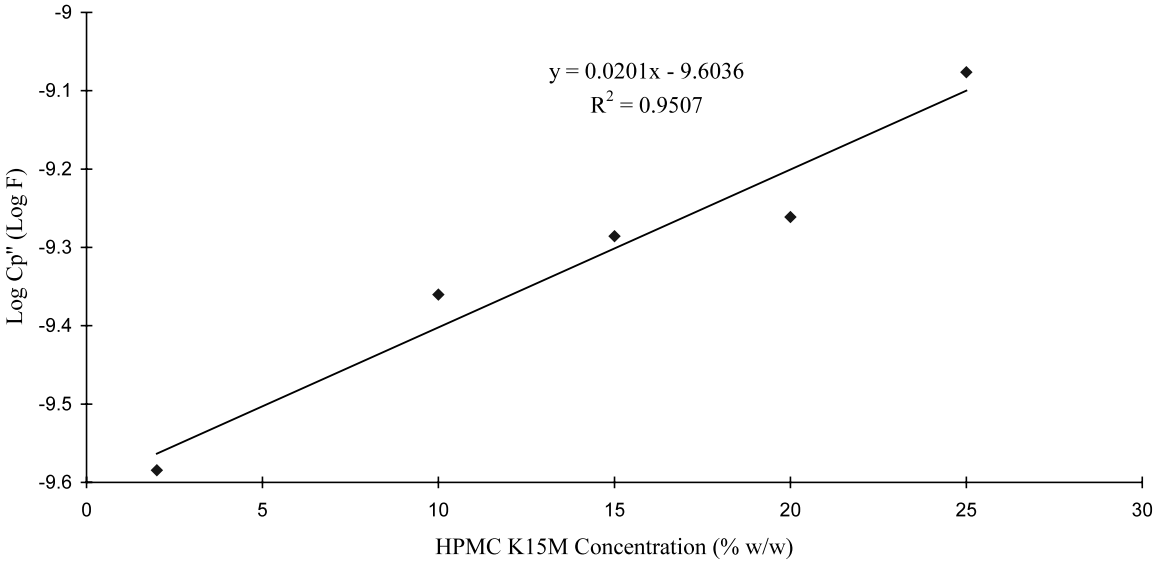

Fig. 6. Log dielectric loss (log Cp″) (log *F*) as a function of concentration for HPMC K15M gels at a frequency of 100 Hz at − 30 °C ($n = 2$).

ing of frozen water appears to begin in the gels varies with polymer molecular weight. Additionally, the pattern of melting as observed by the dielectric response, is somewhat different for HPMC K100LV in comparison to the three other K-series polymers studied. Similarly, in DSC studies, the appearance of endothermic events varied between HPMCs of different molecular weights,

however no specific trend was apparent. HPMC K100LV gels show a series of transitions during the melting process which are quite exaggerated in comparison with such transitions in other gels. The magnitude of the dielectric response in the gels studied vary to a large extent, but these may be related to the presence of different concentrations of ionic species. For example, the increased magnitude of the responses for HPMC K100LV may be explained by the higher percentage of NaCl levels (0.49%) than HPMC K4M (0.36%), HPMC K15M (0.16%) or HPMC K100M (0.28%), respectively.

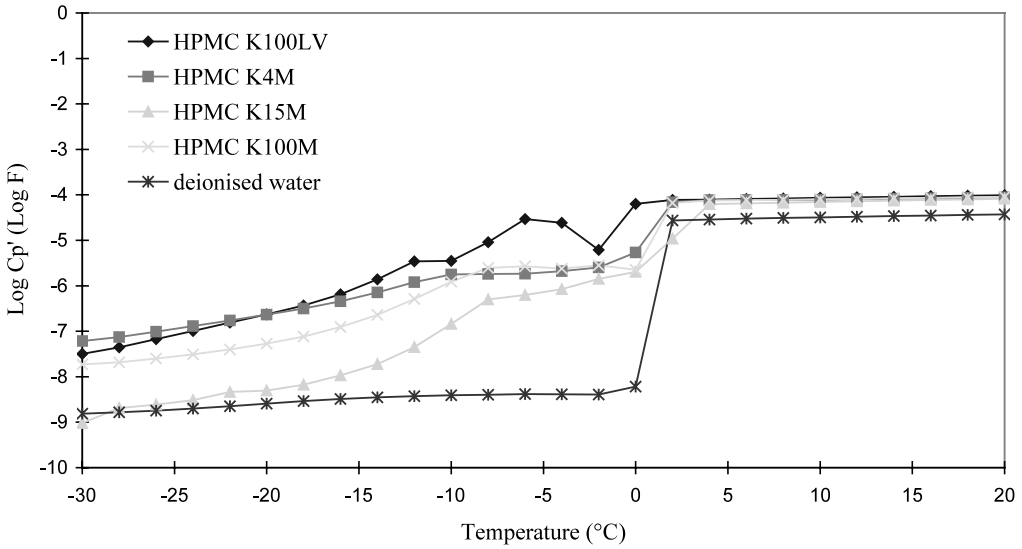

Fig. 7. Log capacitance (log Cp′) (log *F*) against temperature (°C) for 25% (w/w) HPMC K100LV, K4M, K15M and K100M gels and deionised water at a frequency of 1 Hz.

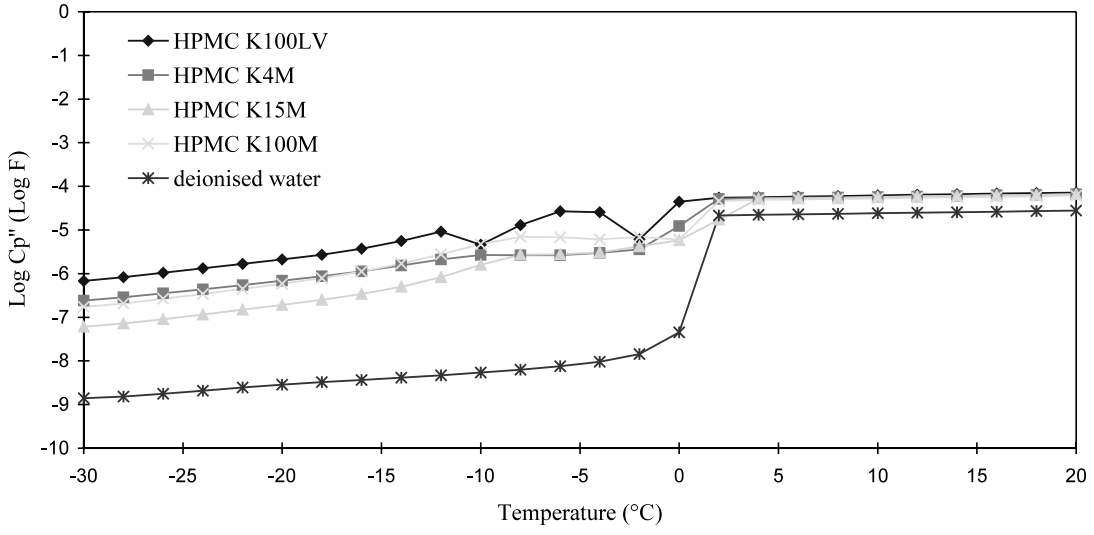

Fig. 8. Log dielectric loss (log Cp″) (log *F*) against temperature (°C) for 25% (w/w) HPMC K100LV, K4M, K15M and K100M gels and deionised water at a frequency of 1 Hz.

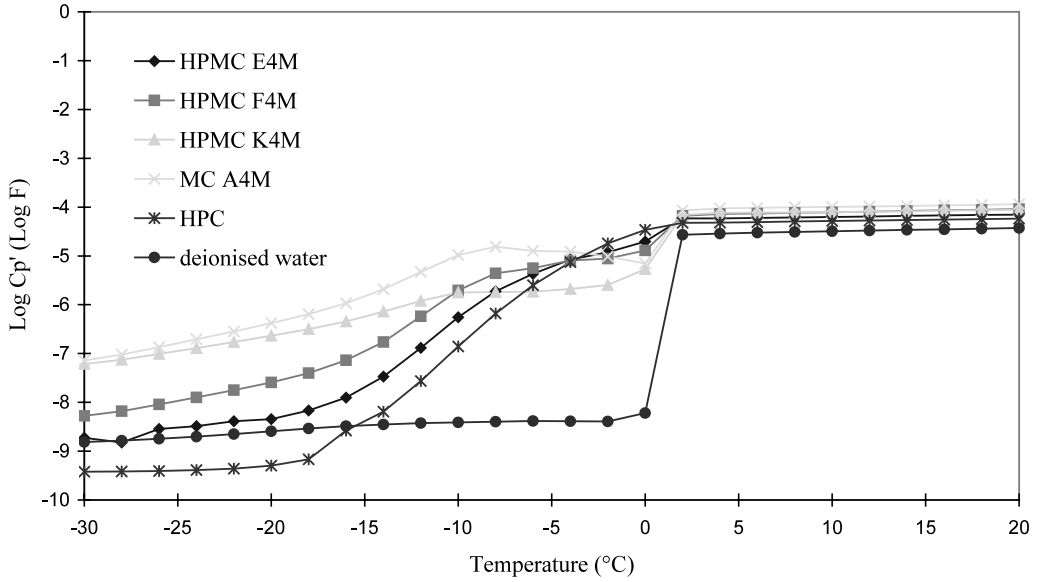

Fig. 9. Log capacitance (log Cp′) (log *F*) against temperature (°C) for 25% (w/w) HPMC E4M, F4M, K4M, MC A4M and HPC gels and deionised water at a frequency of 1 Hz.

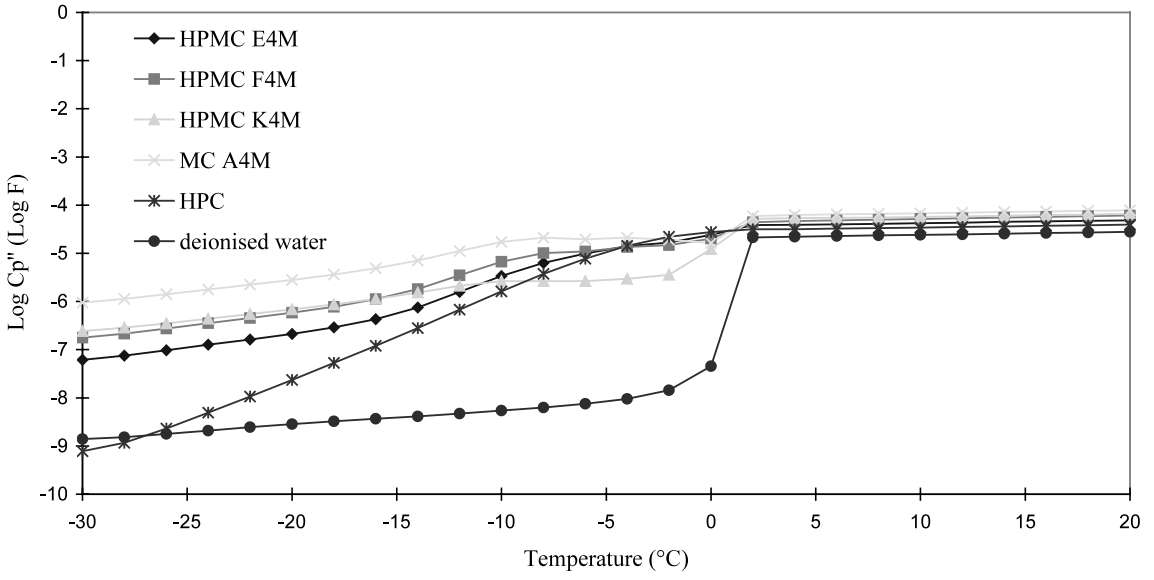

Fig. 10. Log dielectric loss (log Cp″) (log *F*) against temperature (°C) for 25% (w/w) HPMC E4M, F4M, K4M, MC A4M and HPC gels and deionised water at a frequency of 1 Hz.

3.3. The influence of polymer substitution level on the dielectric response of cellulose ether gels

Figs. 9 and 10 show the dielectric spectra of a series of polymers of similar molecular weight but with different substitution types and levels at a frequency of 1 Hz. Their dielectric response over a temperature range of -30 to $+20$ °C clearly varies with polymer substitution level. The magnitude of both the capacitance and dielectric loss

responses vary in a similar pattern within the polymer range studied at both frequencies. This may be related to the level of ionic species in the gel samples. MC Methocel A4M has the highest level of NaCl levels (0.75%), while HPC has no reported NaCl. The magnitude of the dielectric response follows NaCl levels for each of the polymer samples sequentially.

DSC studies on 25% (w/w) HPC gels showed that the melting of ice occurs as a single event with no evidence of any loosely bound water (McCrystal et al., 1997b). The dielectric response in the region where ice melts in HPC gels shows a gradual transition in comparison with the other polymers analysed which show a two stage transition. This may indicate, similar to DSC studies, that the distribution of water in 25% (w/w) HPC gels is different in comparison to the water distribution in gels of other cellulose ethers studied here.

3.4. Effect of drug addition on the nature of the dielectric response in HPMC K15M gels

DSC studies (McCrystal et al., 1997b) have shown that addition of both P.H. and DIC Na affects the distribution of bound water within HPMC K15M gels. Addition of these drugs affected the nature of the transitions visible on the leading edge of the main endotherm for the melting of free water. Figs. 11 and 12 show the dielectric response of deionised water and HPMC K15M gels in the absence or presence of P.H. and DIC Na at a frequency of 1 Hz over a temperature range of -30 to $+20$ °C. Drug addition clearly has an effect on the transitions occurring during the melting of ice in the gels. The magnitude of the dielectric response is increased in gels containing P.H. in comparison to the response seen in gels containing DIC Na in both the capacitance and dielectric loss spectra at both frequencies studied. It is possible that the molar ratio of ionic species released upon dissociation of each drug may differ with DIC Na releasing less ionic species and showing a reduced dielectric response.

Fig. 13 shows the effect of drug addition on the capacitance and dielectric loss of 25% (w/w) HPMC K15M gels in the frequency range of 10^{-2}

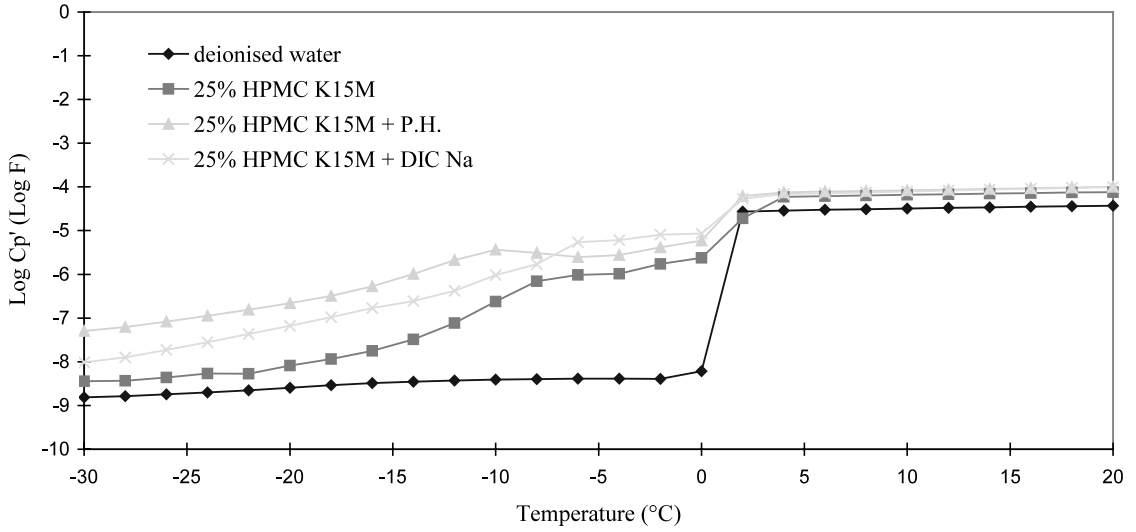

Fig. 11. Log capacitance (log Cp′) (log *F*) against temperature (°C) for HPMC K15M gels alone and in the presence of P.H. (50 mM) and DIC Na (50 mM) at a frequency of 1 Hz.

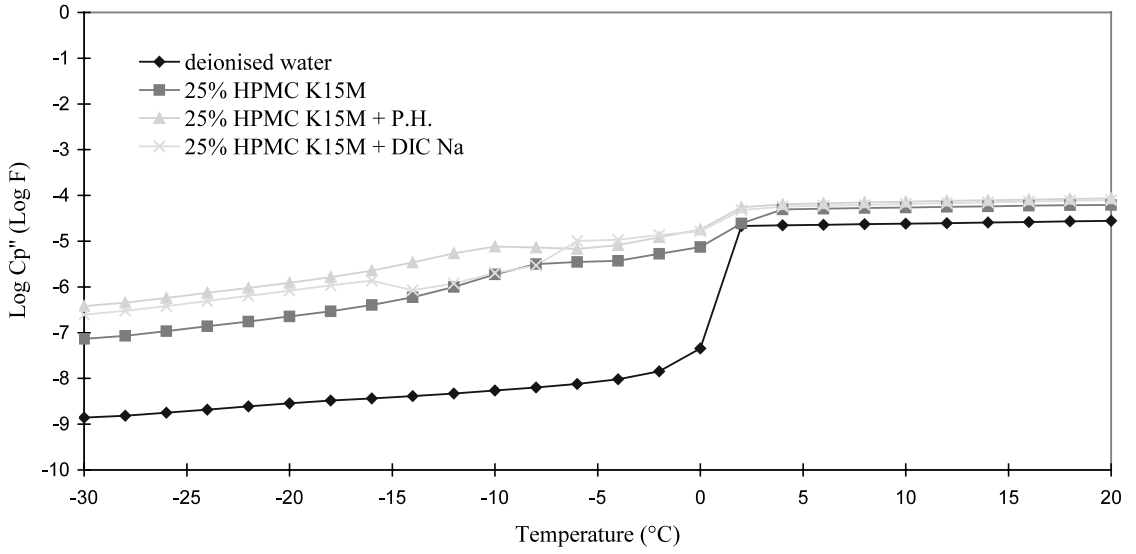

Fig. 12. Log dielectric loss (log Cp″) (log *F*) against temperature (°C) for HPMC K15M gels alone and in the presence of P.H. (50 mM) and DIC Na (50 mM) at a frequency of 1 Hz.

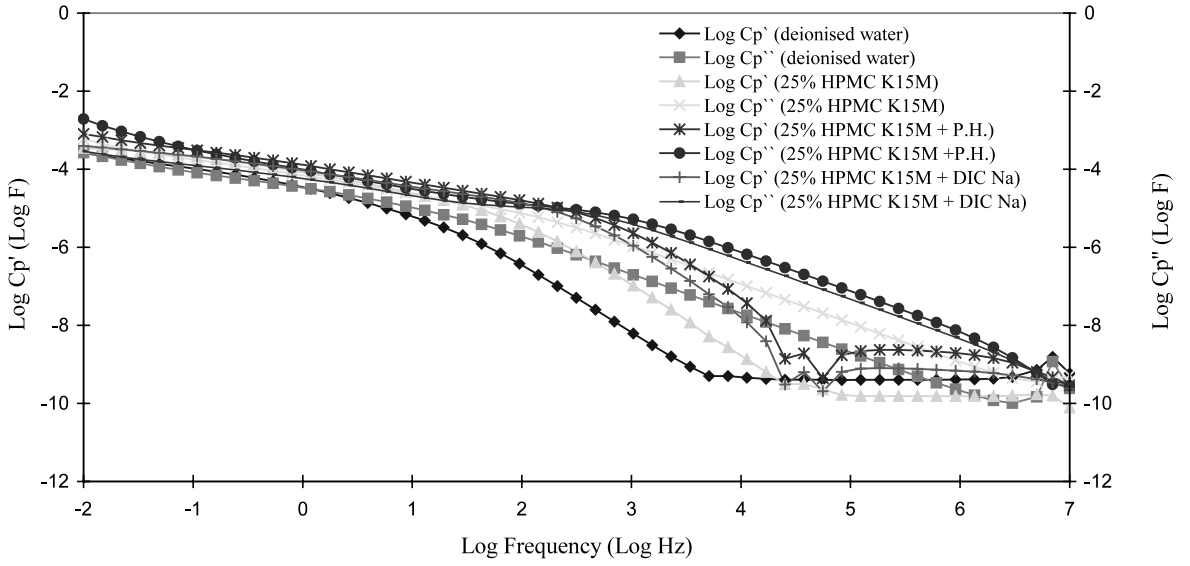

Fig. 13. Log capacitance (log Cp′) and log dielectric loss (log Cp″) against log frequency (log Hz) for deionised water and 25% (w/w) HPMC K15M gels in the absence and presence of P.H. and DIC Na at 22 °C.

to 10^{+7} Hz at 22 °C. The nature of the dielectric response in HPMC K15M gels, which include either P.H. or DIC Na is different, when compared to the dielectric response of deionised water or HPMC K15M gels in the absence of drug. An increase in magnitude of both the capacitance (log Cp′) and dielectric loss (log Cp″) values occurs in the presence of added drugs. This increase in magnitude is greater in HPMC K15M gels containing P.H. which is consistent with the re-

sponse previously seen in temperature scans at constant frequencies. A similar pattern is seen for 25% (w/w) HPMC K15M gels in the frequency range of 10^{-2} to 10^{+7} Hz at 0 °C. However, when such gel systems are analysed at −30 °C as shown in Fig. 14, the magnitude and nature of the dielectric response both changed. The magnitude of the dielectric response is reduced which is consistent with a reduction in the mobility of dipoles in the system with reduction in temperature. A peak is present at 10^3 Hz in the capacitance response of HPMC K15M gels in the presence of P.H. at −30 °C.

4. Conclusions

Low frequency dielectric spectra of HPMC gels from −30 to +20 °C showed that there are several phase transitions, as a result of melting processes, starting at temperatures around −22 °C compared to a single phase transition at about 0 °C for deionised water. These data were found to be in agreement with findings by DSC which have identified more than one event occurring during the melting of ice in HPMC K15M gels of a similar concentration. These events were related to the presence of different states of water, melting at different temperatures in the gel systems.

Frequency scans from 10^{-2} to 10^{+7} Hz at temperatures of +22, 0 and −30 °C showed that deionised water and gel samples scanned at −30 °C gave very different dielectric behaviour compared to the response at higher temperatures. The decrease in magnitude of the dielectric response which occurs at −30 °C was related to the reduction in mobility of dipoles in the system as the sample freezes.

Although all Methocel gels clearly showed multiple phase transitions, indicative of the presence of different states of water, the temperatures at which these transitions occurred and also the magnitude of the dielectric response were influenced by polymer concentration, polymer molecular weight and substitution level. The magnitude of the dielectric response varied according to the levels of ionic species levels in the gel samples.

Drug addition clearly has an effect on the melting of water within HPMC K15M gels as seen by the nature of the dielectric response over the low temperature range where ice melts within the gels.

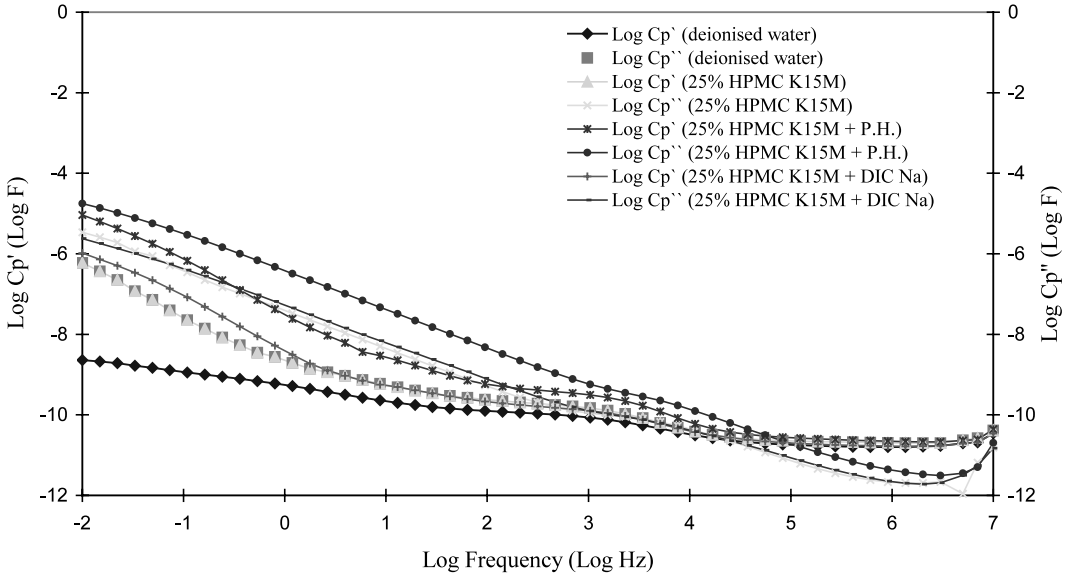

Fig. 14. Log capacitance (log Cp′) and log dielectric loss (log Cp″) against log frequency (log Hz) for deionised water and 25% (w/w) HPMC K15M gels in the absence and presence of P.H. and DIC Na at −30 °C.

LFDS studies on cellulose ether gels have provided some interesting evidence for the existence of more than one state of water within cellulose ether gel systems. The results are in good agreement with thermal analysis findings on similar gel systems.

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