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A study on the interaction of water and cellulose ethers using differential scanning calorimetry[1]

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Abstract

Differential scanning calorimetry (DSC) has been used to examine the distribution of water within hydroxypropylmethylcellulose 2208 (HPMC K15M) gels. Thermal events were apparent in the DSC scans of HPMC K15M gels which were dependent on their storage time, the concentration of the polymer and the cooling and heating rates utilised during DSC. Two or more thermal events were present on the low temperature side of the melting endotherm for gels (20–35% w/w HPMC K15M) in the −15 to 0°C range. These may indicate the presence of different types of water in the gels. The number of moles of non-freezing water per polymer repeating unit HPMC K15M was estimated for gels as ~8 mol after 24 h and ~3.8 mol after 96 h storage. It is suggested that hydrating water is released from the polymer during equilibration between 24 and 96 h storage. © 1997 Elsevier Science B.V.

Keywords: DSC; Hydroxypropylmethylcellulose (HPMC); Water distribution

1. Introduction

The majority of polymers which are used as drug-carrier systems are employed in aqueous environments. The interaction of water with such polymers and its distribution within polymeric systems are critical to their properties such as solution rheology, adhesion, sol–gel transformation [1,2] and also their use in controlled drug-release matrices [3]. The rate at which water diffuses into hydrophilic matrices and forms the barrier gel layer [4,5] and consequent water diffusion through this gel layer are major factors which determine drug-release rate from such devices [6]. Detailed studies on the gel layer and, more specifically, on the types of water that exist within the gel are fundamental to the optimisation and prediction of drug release from these matrices.

The states of water in many polymers have been studied widely and, indeed, there is some debate with regard to the exact number and types of water which exist in polymer gels. The majority of workers have classified three different types of water in hydrophilic polymer gels [7–17]. The types are free (or unbound) water, freezing bound water and bound (or non-freezing) water. Free water may be categorised as unbound water in polymers. Its transition enthalpy and peak shape in differential scanning calorimetry (DSC) curves are equal to those of pure (bulk) water [18]. Bound water is strongly associated with the hydrophillic group of a polymer, and freezing bound water is characterised as having a phase-transition temperature lower than that of bulk water due to a weak interaction with the polymer chain [19].

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In a study of the states of water in cellulose acetate membranes, Taniguchi and Horigome [19] suggested that there are four types of water in hydrophilic polymer gels. These are: free water; free water very weakly interacting with the polymer; bound water which can contain salts; and bound water which rejects salts.

In contrast to the popular models mentioned already, Roorda et al. [20,21] in studies on poly(hydroxyethylmethacrylate) (pHEMA) gels have cast doubts on the existence of three (or more) thermodynamically different classes of water. They have claimed the existence of a single class of water in pHEMA gels. This work was further extended by Bouwstra et al. [22], where they showed that the amount of non-freezable water cannot be explained by different types of water, but is based either on restricted diffusion of water in hydrogels or restriction of a further growth of ice crystals after the transition of the hydrogel from the rubber to the vitreous state.

Various methods have been used in the study of the different states of water in polymeric gels. These include nuclear magnetic resonance (NMR) [7,10,13], DSC [11,12,15,16,18,23–25], differential thermal analysis (DTA) [11,22], thermogravimetric analysis (TG) [11], dilatometry [14] and solute exclusion [26].

The present study concerns the interaction between water and hydroxypropylmethylcellulose (HPMC). DSC has been used to examine the nature of this interaction and the distribution of water within HPMC gels.

2. Experimental

2.1. Materials

Hydroxypropylmethylcellulose 2208 (Methocel K15M; DOW Chemicals, USA) was used.

2.2. Differential scanning calorimetry

A Perkin–Elmer differential scanning calorimeter DSC7 (Beaconsfield, UK) with an attached liquid-nitrogen based cooling accessory controlled by a Perkin–Elmer TAC-7 was employed. Calibrations with indium and zinc were carried out each time the heating rate was changed. Gel samples of 5–15 mg were analysed in aluminium sample pans (40 μl, Perkin–Elmer, Beaconsfield, UK). Cooling rates were varied from rapid cooling to -1°C min^{-1}. In the case of rapid cooling, the DSC head was cooled to -30°C and the sample pan placed on the DSC head providing rapid cooling of the sample. Heating rates varied from $+1$°C min^{-1} to $+100$°C min^{-1}. The specific heating and cooling rates employed are documented in Section 3.

2.3. Gel preparation

HPMC gel (10% w/w, 50 g samples) were prepared by heating half of the total quantity of distilled water required to 80°C, and adding to the previously weighed powdered cellulose ether. The mixture was stirred vigorously to ensure thorough wetting, using an IKA–WERK stirrer (Janke and Kunkel GmbH, Germany). The remaining quantity of water (distilled) was added cold, in stages, and stirring was maintained for 20 min. HPMC gels (20% w/w, 50 g samples) were prepared by heating the full quantity of distilled water to 80°C and then adding the previously weighed cellulose ether directly to the water while stirring for 20 min, using a magnetic hot plate stirrer. All gels were stored at 4°C and water losses during both preparation and storage were taken into account when determining the final polymer concentrations in the gels.

2.4. Preparation of gel samples with different polymer : water ratios

A series of gel samples containing 20 to 55% w/w HPMC were prepared using HPMC K15M. Initially, gels were prepared as detailed in Section 2.3 and stored at 4°C for 24 h. A series of ~15 mg samples of the gels were weighed into DSC sample pans and heated at 55°C in an oven. The samples were removed after varying storage times, reweighed and sealed. The exact polymer : water ratios were calculated using the initial weight and the amount of moisture lost during heating. The sealed DSC pans were stored for 24 or 96 h at ambient temperatures to allow equilibration and uniform water distribution in the gel before analysis.

The effect of cooling and heating rates on the nature of DSC endothermic and exothermic events in HPMC

K15M gels were studied using gel concentrations of 25 to 35% w/w, where secondary events were most exaggerated.

3. Results and discussion

3.1. Characterisation of HPMC gels using DSC analysis

Samples of gels containing 20% w/w HPMC K15M were stored at 4°C for 2 and 24 h. They were then cooled from +35° to −30°C at a variety of cooling rates (rapid cooling to $-5^{\circ}\mathrm{C\,min^{-1}}$) and, subsequently, heated to +35°C at $10^{\circ}\mathrm{C\,min^{-1}}$. No pre-endothermic events were visible at any cooling rate for gels stored for 2 h. However, a number of pre-endothermic events were visible in the case of 20% w/w HPMC K15M gels stored for 24 h (Fig. 1). It is evident from the standard deviations in Table 1, that the enthalpies for gels stored for 2 h showed a much wider spread than the data obtained for 24 h samples. Gel samples after 2 h storage may not have been homogeneous, and therefore insufficient time was allowed for equilibration. It may be assumed that the DSC peaks in these samples represent the bulk water with little or no influence from the polymer. These results are in contrast to those reported by Ford and Mitchell [28], where the melting enthalpies increased as the storage time of HPMC K15M gels increased over a similar time period. Batch to batch variation and, indeed, an exact method of gel preparation may be contributing factors towards this apparent anomaly.

It was suspected that such pre-endothermic events may be related to the presence of different water types in the HPMC K15M gels studied and thus the effects of the gel storage time and concentration were investigated further in an attempt to characterise such pre-endothermic events. Samples of gels containing 10 or 20% w/w HPMC K15M were stored at 4°C for 96 h. Typical scans are shown in Fig. 1. A pre-endothermic event was visible at all cooling rates in the case of gels containing 20% w/w HPMC K15M. No such event(s) were apparent for gels containing 10% w/w HPMC K15M.

Thus far, it has been established that the concentration of HPMC K15M is a contributing factor to the type and number of endothermic peaks which are visible in the DSC scans. This concentration anomaly was further explored by preparing a series of gels in which the polymer concentrations were varied. Sam-

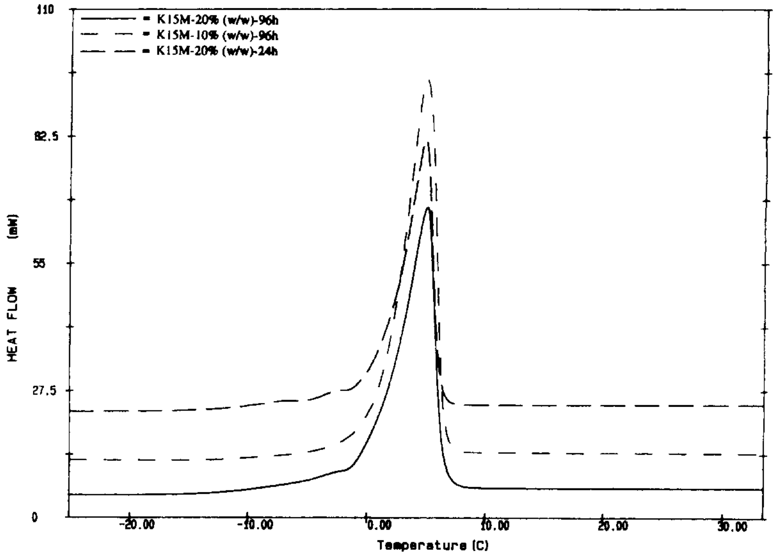

Fig. 1. DSC scan of HPMC K15M 20% w/w gel stored for 24 h at a heating rate of $+10^{\circ}\mathrm{C\,min^{-1}}$ (top). DSC scans of HPMC K15M 10% w/w and HPMC K15M 20% w/w gels, after 96 h storage, scanned at a heating rate of $+10^{\circ}\mathrm{C\,min^{-1}}$, indicating the appearance of a pre-endothermic event at the higher concentration (bottom scans).

Table 1
Effect of cooling rate (°C min^{-1}) and gel storage time (h) on the melting enthalpy of HPMC K15M 20% w/w gels

Cooling rate	Enthalpy in Jg^{-1}	
(°C min^{-1})	2 h old samples	24 h old samples
Flash	251.2 ± 7.4	206.0 ± 8.5
−100	271.2 ± 28.3	232.4 ± 8.3
−10	253.1 ± 13.0	205.3 ± 14.6
−5	261.4 ± 42.4	196.8 ± 0.7

ples containing different polymer concentrations were prepared, stored for either 24 or 96 h and analysed. Typical DSC scans for 96 h-old HPMC K15M gels of different concentrations are shown in Fig. 2. More than one event is clearly apparent on the endotherms of gels containing more than 10% w/w polymer. These events were more exaggerated at the higher polymer concentrations. Similar events were visible in 24 h-old samples.

3.2. Number of moles of non-freezing water per polymer repeating unit of HPMC K15M

The number of moles of non-freezing water per polymer repeating unit (PRU) was determined according to the procedure reported by Ford and Mitchell [28]. Enthalpy change (J g^{-1}) was plotted against % water content for HPMC K15M gels cooled to −30°C at −100°C min^{-1} and heated to +35°C min at +10°C min^{-1} after 24 and 96 h storage (Fig. 3). The plots were extrapolated to zero enthalpy through the lines of best fit, where the concentration is the minimum water : HPMC ratio required for water to occupy the binding sites of HPMC K15M, giving complete hydration. All water present at this point was taken as bound water. For the basis of this calculation, it is assumed that a linear relationship exists between enthalpy of melting and % water over the full range of polymer concentrations used in this work; however, this assumption may not apply at higher polymer concentrations. The % ratios of HPMC K15M : water at zero enthalpy were found to be 58 : 42 after 24 h ($r^2 = 0.588$) and 74 : 26 after 96 h storage ($r^2 = 0.961$).

The number of moles of non-freezing water per polymer repeating unit (PRU) were calculated using these data and the previously quoted PRU value of 192 for HPMC K15M [28]. These values were ~8 and ~3.8 mol for 24 and 96 h storage times, respectively.

These results show that less bound (and, hence more free) water is present after 96- compared to 24 h-old samples. This is in contrast to data obtained for HPMC K15M 20% w/w gels stored for 2 and 24 h, respec-

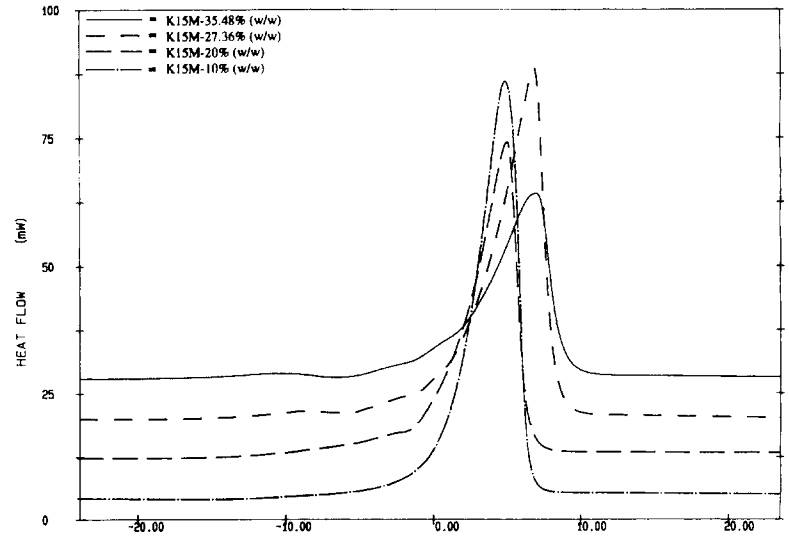

Fig. 2. DSC scans of HPMC K15M gels stored for 96 h, showing the effect of concentration of endothermic events at a +10°C min^{-1} heating rate.

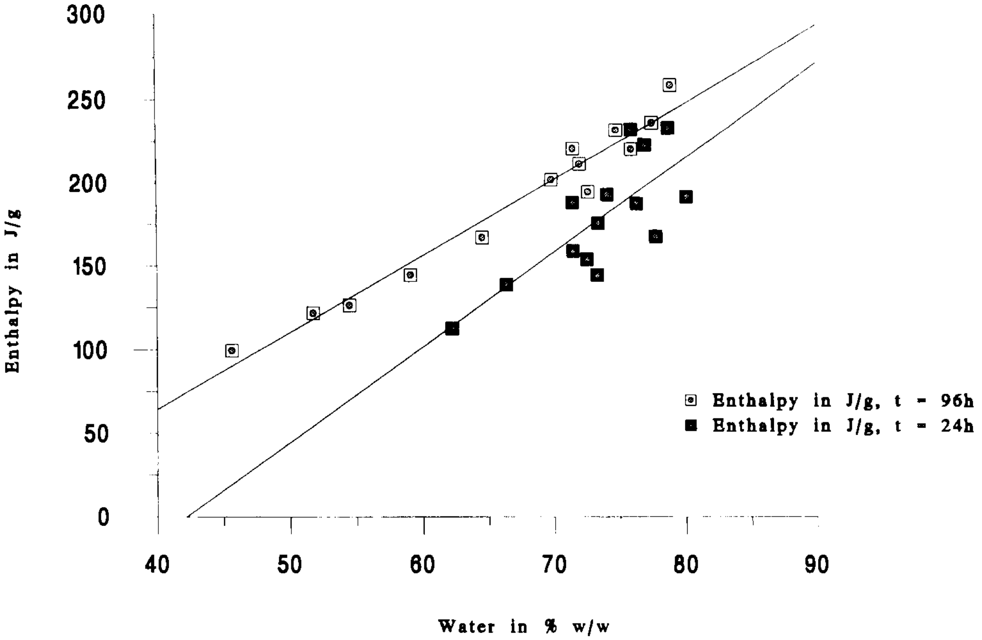

Fig. 3. The effect of water content (% w/w) on the melting enthalpy (J g^{-1}) of HPMC K15M gels after storage for 24 or 96 h.

tively (Table 1). This may suggest that the hydrating water is released from the polymer during storage between 24 and 96 h due to gel syneresis [27]. The decrease in free water which occurs between 2 and 24 h may be attributed to initial equilibration within the gel as some free water becomes more tightly bound to the polymer.

3.3. Investigation of cooling and heating rate anomalies

The occurrence of anomalies around the endotherm produced by the melting of water at 0°C has previously been reported by Nakamura et al. [12], who showed that on DSC heating runs of various cellulose samples, a shoulder existed in some cases on the leading edge of the endotherm. Sung [13] has also reported the presence of a double endotherm at 0°C in poly(2-hydroxyethylmethacrylate) (pHEMA) hydrogels, whose shape was dependent on the freezing conditions. This was attributed to the presence of three different types of water in the hydrogels. The double peak was attributed to free and 'intermediate' water, with the bound water being tightly attached to the polymer and not freezing. Hatakeyama et al. [24] have reported the presence of a smaller peak to the high-temperature side of the melting endotherm at 0°C as well as the presence of a sub-melting peak or shoulder on the low-temperature side in representative polyelectrolyte–water systems. The small peak appearing at the high-temperature side of the main melting peak in such systems was attributed to the transition from the liquid crystalline state to the liquid state of bound water [24]. The sub-melting peak or shoulder on the low-temperature side was not explained.

After investigation of the effect of gel concentration and storage time anomalies, it would seem logical that if the visible pre-endothermic events were indeed related to different types of water, heating and cooling rates during DSC analysis may have some effect on the nature of such events.

3.3.1. Cooling rate variation

The enthalpies of fusion and crystallization temperatures for samples stored for 24 and 96 h were unaffected by cooling rate variations. In the cooling runs, some secondary events were visible (Fig. 4) (peak from −22.90° to −26.65°C). However, such data were not reproducible. More than one peak on the

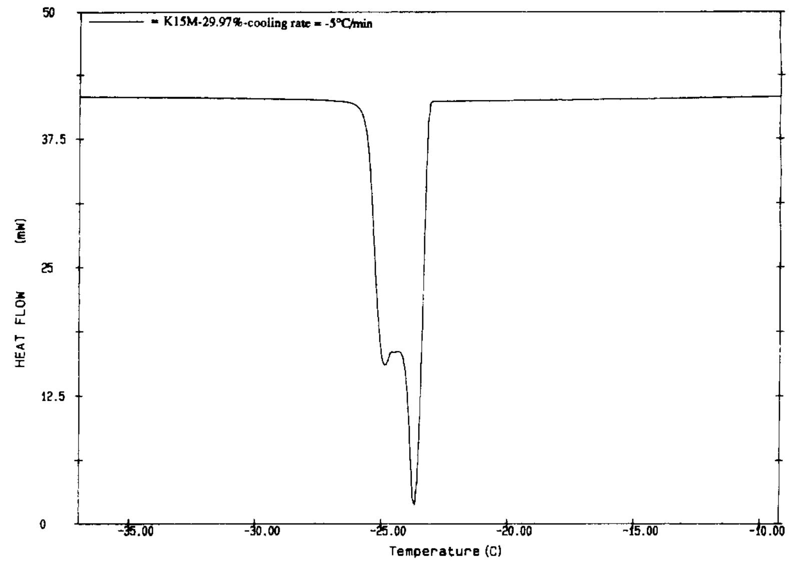

Fig. 4. DSC cooling curve of HPMC K15M 29.97% w/w gel at a –5°C min^{-1} cooling rate after 24 h storage.

cooling run may indicate different types of water crystallizing at slightly different temperatures. In the heating runs (+10°C min^{-1}), it was found that the secondary events were cooling-rate dependent. At low cooling rates, e.g. –5°C min^{-1}, a small endotherm appearing to the left of the main peak was exaggerated (Fig. 5) (initial peak from –6.84° to +3.74°C). Other events were also visible on the leading edge of the main endotherm. As the cooling rate increased, the initial small endotherms were not as exaggerated. However, the other events on the main endotherm remained visible.

3.3.2. Heating rate variation

The enthalpies of fusion and crystallization values for samples stored for both 24 and 96 h were unaf-

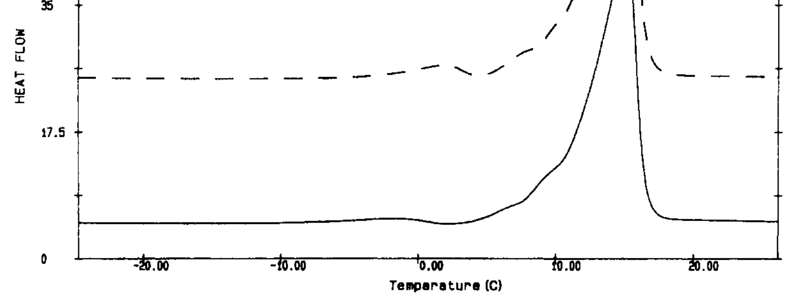

Fig. 5. DSC scans of HPMC K15M gels after 96 h storage following cooling at –50° or –5°C min^{-1}.

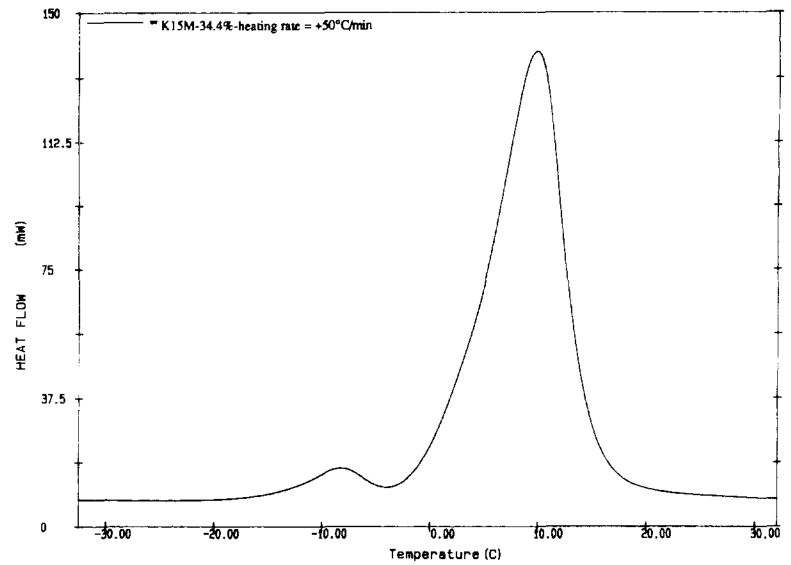

Fig. 6. DSC scan of HPMC K15M gel stored for 24 h at a heating rate of +50°C min^{-1} following cooling at -10°C min^{-1}.

fected by heating rate variations. In the cooling runs (-10°C min^{-1}), some secondary events were found to be visible but they were irreproducible. At a heating rate of +50°C min^{-1}, an initial small endotherm is clearly seen (Fig. 6). As the heating rate was decreased (+1°C min^{-1}), this initial endotherm was not as exaggerated and other inflections become more evident on the main endotherm (Fig. 7).

At the molecular level, a very low cooling rate would allow the associated water to freeze slowly and combine more tightly with the polymer. In a constantly changing dynamic situation, the amount of bound water will thus tend to increase and will appear as a more pronounced peak to the left of the main endotherm (Fig. 5). The cooling rate will not affect the other smaller undefined peaks or the main

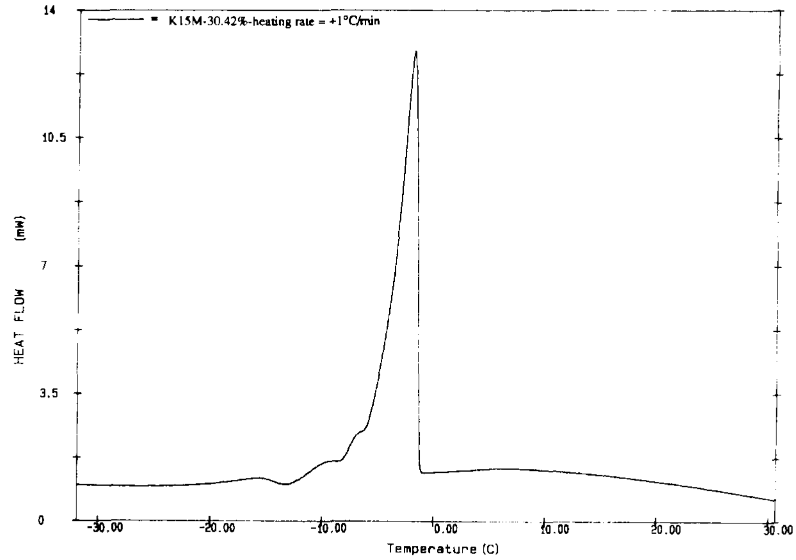

Fig. 7. DSC scan of HPMC K15M gel stored for 24 h at a heating rate of +1°C min^{-1} following cooling at -10°C min^{-1}.

endotherm but may affect this closely associated or type of 'bound' water. If this pronounced endotherm indicates the presence of a type of 'bound' water, then the other small events visible on the leading edge of the main endotherm may be considered as other, as yet undefined, types of water. On the other hand, at high heating rates, this closely associated water tends to come off as a single small endotherm towards the lower temperature side of the main peak (Fig. 6). When the heating rate is lower, this water comes off as a number of separate events, possibly, indicating the presence of more than one type of closely associated water (Fig. 7). It is apparent, looking at Fig. 6, that some recrystallization may be occurring between the two main melting events. This however does not contradict the assumption that different types of water may be present which melt at different temperatures. It is also worth considering that these events occurring on the low temperature side of the main endothermic peak may be due to a mesomorphic transition.

4. Conclusions

Differential scanning calorimetry has been used to carry out studies on HPMC K15M hydrogels in an attempt to learn more about the nature of the interaction between water and the polymer. It was found that the gel storage time, polymer concentration and cooling/heating rate affected the thermal events occurring within the HPMC K15M gels. The number of moles of bound water per polymer repeating unit were ~8 and ~3.8 mol for 24- and 96 h-old HPMC K15M gels, respectively. The appearance of multiple events on the low-temperature side of the main melting endotherm may be related to the presence of different types of bound water within HPMC K15M gels.

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