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Thermal analysis of hydroxypropylmethylcellulose and methylcellulose: powders, gels and matrix tablets

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Abstract

This review focuses on the thermal analysis of hydroxypropylmethylcellulose (HPMC) and methylcellulose. Differential scanning calorimetry (DSC) of their powders is used to determine temperatures of moisture loss (in conjunction with thermogravimetric analysis) and glass transition temperatures. However, sample preparation and encapsulation affect the values obtained. The interaction of these cellulose ethers with water is evaluated by DSC. Water is added to the powder directly in DSC pans or preformed gels can be evaluated. Data quality depends on previous thermal history but estimates of the quantity of water bound to the polymers may be made. Water uptake by cellulose ethers may be evaluated by the use of polymeric wafers and by following loss of free water, over a series of timed curves, into wafers in contact with water. Cloud points, which assess the reduction of polymer solubility with increase of temperature, may be assessed spectrophotometrically. DSC and rheometric studies are used to follow thermogelation, a process involving hydrophobic interaction between partly hydrated polymeric chains. The advantages and disadvantages of the various methodologies are highlighted.

Keywords: Hydroxypropylmethylcellulose; Methylcellulose; Differential scanning calorimetry; Thermal mechanical analysis; Glass transition temperature; Gelation; Cloud point

1. Introduction

Cellulose ethers, especially hydroxypropylmethylcellulose (HPMC), are frequently used as the basis for sustained release hydrophilic matrix tablets. Despite studies in the 1960s describing their uses (Lapidus and Lordi, 1966, 1968), their characterisation and performance have been more extensively quantified recently. Most studies have been performed on four non-ionic methylated derivatives of cellulose ethers. These have differ-

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ent substitution levels and are methylcellulose, hydroxypropylmethylcellulose E type (HPMC 2910), hydroxypropylmethylcellulose F type (HPMC 2906) and hydroxypropylmethylcellulose K type (HPMC 2208). Their chemical substitutions are summarised in Table 1. They are available in a wide range of molecular weights and are classified on the basis of the viscosities of their 2% w/w aqueous solutions. For example, 2% w/w solutions of HPMC K100 and HPMC K15M have nominal viscosities of 100 and 15 000 cps, respectively.

Matrices containing cellulose ethers prolong drug release by rapidly forming a protective viscous layer around the tablet surface when exposed to aqueous fluids. This hydrated viscous layer controls water penetration into the central dry core of the tablet and prevents disintegration. When cellulose ethers in their matrices are exposed to an aqueous medium, they undergo rapid hydration and chain relaxation (Colombo et al., 1985; Colombo, 1993) to form a viscous gelatinous layer which is commonly termed the 'gel layer', at the surface of the tablet (Rajabi-Siahboomi et al., 1992). Failure to form a uniform and coherent 'gel layer' may cause immediate drug release. It is the subsequent physical characteristics of this 'gel layer' that control water uptake and modify the mechanism of drug release from the matrix. Growth of this 'gel layer' occurs as water permeates through it to hydrate the polymer particles that are immediately beneath it. Concomitantly the outer layers become fully hydrated and dissolve. Water continues to penetrate towards the core of the tablet until all the tablet has dissolved. During water uptake and drug release, the 'gel layer' will contain polymer, drug and excipients experiencing different degrees of hydration or solution (Alderman, 1984). It is generally assumed that water soluble drugs are released primarily through diffusion through the 'gel layer' and that poorly water soluble drugs are primarily released through erosion of the 'gel layer'. In reality, the release mechanism is dictated by the solubility of the drug and both mechanisms contribute to drug release. It is the relative contribution from each process that is controlled by the solubility of a drug (Ford et al., 1987).

Polymers, with hydrophilic groups such as hydroxyl groups, have various strengths of interaction with water (Hatakeyama and Hatakeyama, 1998). The mechanical properties of cellulose ethers are affected by this interaction (Nokhodchi et al., 1996a,b). Water can plasticise the polymer or form stable bridges, through hydrogen bonding resulting, for instance, in the production of strong compacts. The thermal properties of polymers and water are both influenced by this interaction.

This paper reviews the use of thermal analytical methods in characterising the performances of HPMC and methylcellulose and examines the thermal analysis of the polymers alone, their hydration and water up-takes, and their interactions with water as powders or as matrices.

Table 1
Chemical substitution of Methocel™ cellulose ethers

Type	% Methoxyl[a]	% Hydroxypropoxyl[a]	USP type
Methocel A	27.5–31.5 (30)[b]	0	MC
Methocel E	28–30 (29)	7–12 (8.5)	HPMC 2910
Methocel F	27–30 (28)	4–7.5 (5.0)	HPMC 2906
Methocel K	19–24 (22)	7–12 (8.1)	HPMC 2208

[a] DOW Chemical Co. limits.
[b] USP limits in parentheses.

2. Thermal analysis of methylcellulose and hydroxypropylmethylcellulose powders

Differential scanning calorimetry (DSC) of a powder is normally accomplished in aluminium sample pans. Inevitably, on examining the polymer, some water will be associated even in the dry state with the powder. In normally sealed pans, HPMC or methylcellulose display a broad endotherm at 60–140°C, corresponding to moisture loss (Fig. 1). The precise temperature range de-

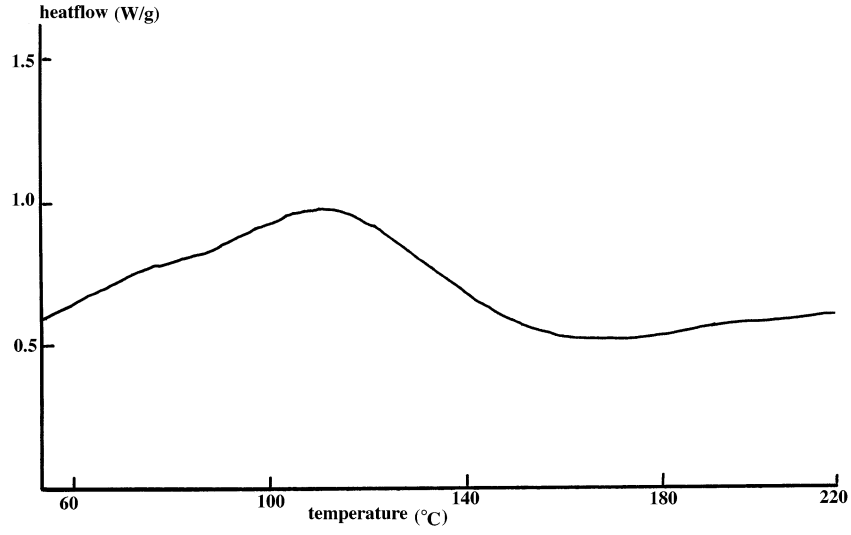

Fig. 1. DSC curve of a sample of hydroxypropylmethylcellulose E4M (~ 1 mg) obtained using a crimped and fully sealed aluminium sample pan at a heating rate of 20°C min^{-1}.

pends on the integrity of the seal of the pan. Pin-holed lids will reduce the temperature at which this moisture is lost and the use of hermetically sealed pans may result in an increase in this temperature. Such dependence of thermal events on sample encapsulation should always be considered when examining polymers containing relatively labile water. Curves obtained by thermogravimetric analysis (TGA) show a rapid moisture loss from ambient to 70°C (Fig. 2) in open pans indicating the thermolability of the moisture even at low temperatures and the relative stability of the dried polymer as the temperature is raised to 200°C. The moisture loss transitions in Figs. 1 and 2 do not, because of the different sample preparations, occur at equivalent temperature.

McCrystal (1998) determined the glass transition temperature (Tg) of various HPMC polymers using large volume stainless steel cells (50 μl) and larger weights of polymer (~ 18 to ~ 30 mg). Under these conditions the temperature at which water desorption occurred was reduced and the glass transition was more readily apparent (Fig. 3). The large volume cells reduced the interference that was possibly caused by particle movement in the smaller aluminium cells. Additionally large volume cells will improve the signal to noise ratio by providing a greater sample mass. It should be remembered, however, that HPMCs are not homogenous polymers. Therefore the Tg is not a sharp transition even in fully optimised systems and may occur over a wide temperature range, possibly as large as 30°C. The problems of determining the true Tg, and the use of onset and end temperatures have been discussed previously (Ford and Timmins, 1989).

Because of this associated moisture, the determination of a Tg is difficult. Values for the Tg of HPMC include 180°C obtained by DSC of the powder but 157°C by DSC of a film cast from dichloromethane/methanol (Sakellariou et al., 1985). Torsional braid analysis resulted in a value of 157°C (Sakellariou et al., 1985). Joshi and Wilson (1993) also determined the Tg of HPMC E5 from aqueous-cast films in DSC pans showing it to be 154°C. With a 1% moisture level this value decreased to 152°C and no glass transition was observed for samples containing > 1% water. Hancock and Zografi (1994) examined the theory behind the glass transition of HPMC–water systems. The variation of Tg with water was studied using a Tg of water of − 138°C and a Tg of HPMC of 155°C. The glass transition tempera-

ture is dependent on the amount of moisture in a sample. Moisture not only lowers the temperature at which the transition occurs but also broadens the range over which is it seen, making the transition indiscreet and often difficult to assess. Loss of water during scanning will probably result in a temperature that does not correspond to the Tg of the original sample. Annealing the sample could also result in water loss. A further difficulty is that the Tg may overlap the moisture loss endotherm. Modulated methods of thermal analysis will resolve the two transitions but do not take into account the potential moisture loss from the polymer fibres. Encapsulating the material in stainless steel pans may potentially result in a loss in sensitivity, even when using modulated heat flow techniques.

3. Thermal analysis of HPMC or methylcellulose–water systems

In general, water associated with a polymer can display various types of interaction and at least three types of thermodynamic water are recognised. Type I water, which corresponds to bulk free water, does not interact with the polymer and behaves as normal water in terms of its melting and freezing and may be described as freezing water (Hatakeyama and Hatakeyama, 1998). Type II water is loosely bound to the polymer, displays considerable supercooling and therefore freezes at a temperature lower than that of bulk water. Type II water may display a significantly smaller enthalpy than that of bulk water and may be termed freezing bound water. Type III water is water tightly bound to the polymer and is incapable of freezing. This later water fraction will generally show no first order phase transitions (Hatakeyama and Hatakeyama, 1998) and may be termed non-freezing water. The sum of Types II and III water may be defined as the bound water content.

Some workers, however, believe that the differentiation of these types of thermodynamic water is incorrect and that the interpretation may be a consequence of the thermal treatment of the samples. For instance, Roorda (1994) indicated that the presence of a glass transition, at or close to the temperature of water melting (and freezing) in hydrogels, can be responsible for apparent irregular melting behaviour. This however, does not necessarily indicate the presence of different types of waters in these gels. Both relaxation NMR and differential thermal analysis (DTA) were required to confirm the type of water present. Part of the problem is that crystallisation in hydrogels is a slow process (Roorda, 1994). Therefore annealing at sub-ambient conditions may change the shape of the melting endotherms.

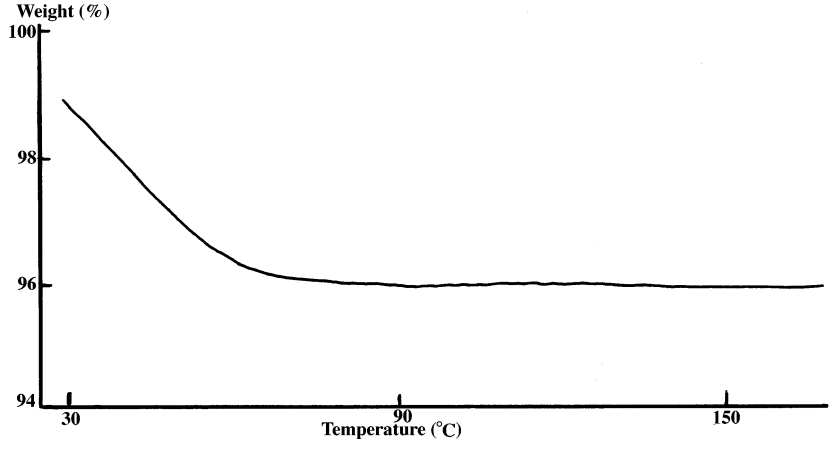

Fig. 2. Thermogravimetic analysis of a sample of hydroxypropylmethylcellulose K4M obtained using an open crucible at a heating rate of 10°C min^{-1}.

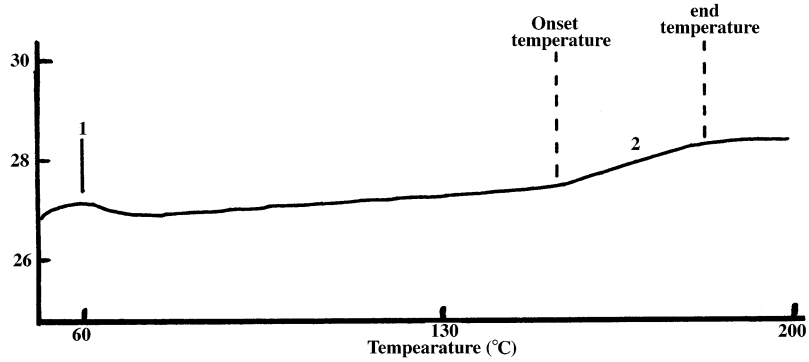

Fig. 3. DSC curve of a sample of hydroxypropylmethylcellulose K4M (~ 20 mg) obtained using sealed stainless steel pans (50 μl) at a heating rate of 10°C min^{-1}. A water loss endotherm around 60°C and a broad glass transition at around 170°C are shown (Reprinted from a Ph.D. Thesis at the John Moores University, Liverpool by C.B. McCrystal, Characterisation of the fundamental interactions between water and cellulose ether polymers, Copyright (1998), with permission from Elsevier Science).

Thermal analysis of cellulose ether gels or powders containing water has been studied over two transitions. Experiments that examine the freezing and melting of water are, by necessity, in the range − 50 to + 10°C. The hydration and dehydration of polymeric gels usually take place in the range 20–80°C. Irrespective of which transition is being examined, care should be taken with the use of aluminium pans in case aluminium hydroxide is formed on their surface (Hatakeyama and Quinn, 1994) for samples containing large quantities of water.

3.1. Transitions in the range − 50 to + 10°C

In the powder form, all water in HPMC or methylcellulose samples will be adsorbed or bound to the polymer surface. Increasing the water content will increase the amount of water bound to the samples, either loosely or strongly, until free or bulk water is apparent. To demonstrate the type of water present, the samples should be scanned through the transitions of the water. Thermal analysis, using cooling and/or heating curves, is a potential approach. If the total amount of water in a polymer–water system is known, for instance it may be determined by weight loss from thermogravimetry or TGA, some estimation of the distribution of water can be determined from cooling and heating DSC curves.

It is generally recommended that the sample be cooled from ambient conditions at 5–10°C min^{-1} to − 120°C, isothermally holding at this temperature, and then re-heating to ambient temperature at similar rates (Hatakeyama and Hatakeyama, 1998). The number and temperature of crystallisation exotherms or melting endotherms depend on the polymer and the water content. Whilst this type of technique produces information for insoluble polymers such as cellulose itself (Nakamura et al., 1981) or sodium carboxymethylcellulose (Bhaskar et al., 1998), it has not been widely applied to HPMC, methylcellulose or their gels. A potential problem is that the amount of free water is determined from a knowledge of the enthalpy of the crystallisation (or melting) peak due to the bulk water in the system and the heat of crystallisation (or melting) of water. These enthalpies are not constant for all water fractions and therefore the value of freezing bound water can not be determined in a similar manner. The heats of fusion and heats of crystallisation do not concur with each other. This will be due to a number of factors including differences in the specific heat of super-cooled water prior to recrystallisation or melting (Joshi and Wilson, 1993) and the fact that the melting enthalpy, although at a maximum value of 334 J g^{-1}, may be between 311 and 334 J g^{-1} because of the formation of various polymorphic forms of ice (Eisenberg and Kauzman, 1969).

Water recrystallisation in gels that are warmed from the frozen state is displayed in events prior to the endotherm corresponding to melting of the main proportion of ice. Murase (1993) reported an endothermic trend preceding an ice recrystallisation exotherm prior to major melting in gels containing cross-linked dextrans. This was attributed to the melting of ice crystals trapped in the polymer network. Similar events (Fig. 4) were seen in gels containing HPMC K15M (McCrystal et al., 1997a). The origin of such events is open to debate. The events may indeed reflect a variety of interactions with the polymer but equally may reflect the size distribution of ice crystals in polymer gels. These depend on the cooling treatment and may be a function of the compartmentalised water entrapped in the polymer network (Murase, 1993). These events, irrespective of their origin, are dependent on the thermal history of the HPMC gels (McCrystal et al. 1997a), e.g. see Figs. 4 and 5. Bouwstra et al. (1995) similarly examined the thermal behaviour of water in hydrogels based on polymethacrylic acids. The amount of non-freezable water could not be explained by different types of water but was based either on a restriction of the diffusion of water in hydrogels or on a restriction of further growth of ice crystals after transformation of the hydrogel from a rubbery state to a glassy state.

The role of a polymer such as HPMC in controlling drug release is determined by its hydration, swelling and dissolution. The latter process involves steps including absorption or adsorption of water at the most accessible sites on the polymer, breaking of polymer–polymer bonds via the creation of water–polymer bonds, separation of the polymer chains and finally dispersion of the polymer chains in the dissolution media (Joshi and Wilson, 1993).

Techniques to evaluate polymer/water interactions may involve pre-formed gels or equilibration of water/HPMC samples weighed separately and sealed in hermetically closed sample pans. Partially hydrated samples were prepared by weighing water into aluminium sample pans containing weighed dry HPMC E5 (Joshi and Wilson, 1993). This technique requires hermetic sample pans AND a period of storage to allow equilibration of

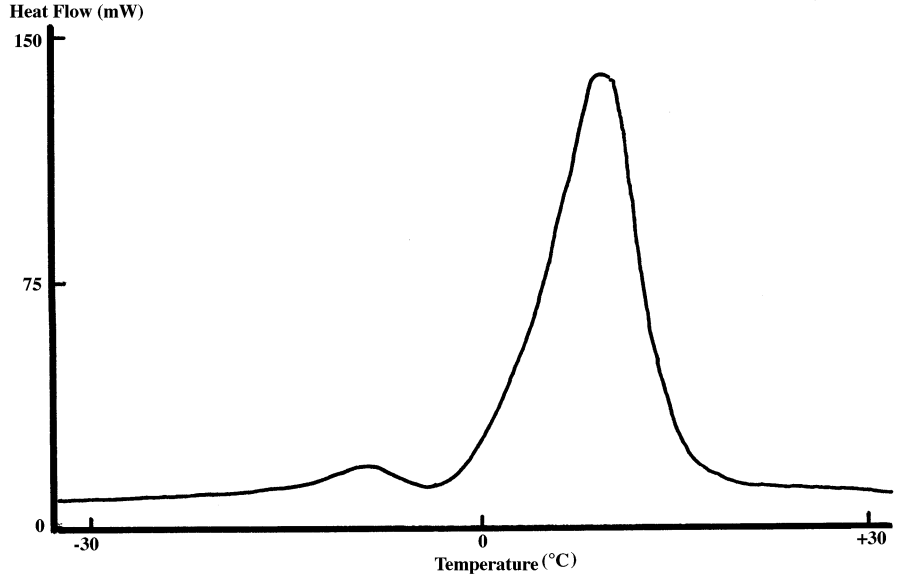

Fig. 4. DSC curve of an aqueous gel containing 34.4% hydroxypropylmethylcellulose K15M obtained using sealed 40 μl aluminium sample pans at a heating rate of 50°C min^{-1} following cooling at 10°C min^{-1} (reprinted from Thermochim. Acta, 294, C.B. McCrystal, J.L. Ford, and A.R. Rajabi-Siahboomi, A study on the interaction of water and cellulose ethers using differential scanning calorimetry p. 97, Copyright (1997), with permission from Elsevier Science).

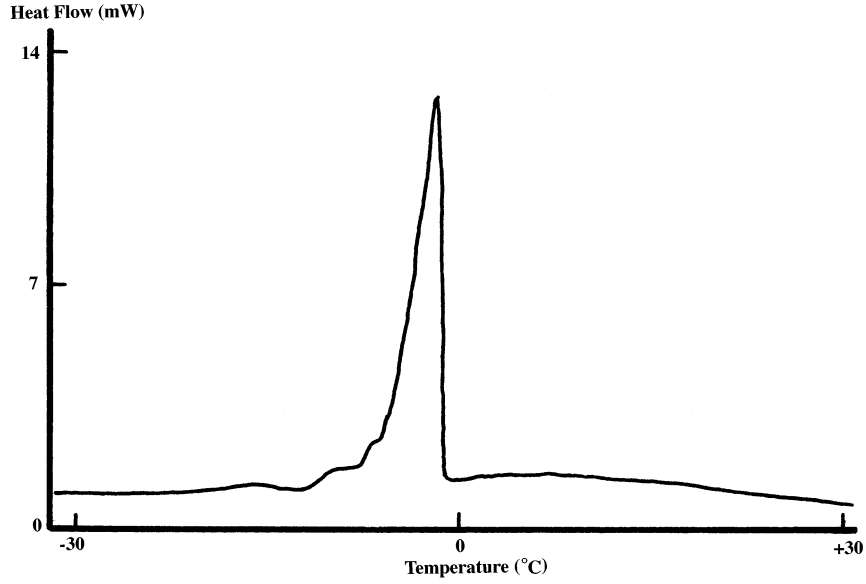

Fig. 5. DSC curve of an aqueous gel containing 30.4% hydroxypropylmethylcellulose K15M obtained using sealed 40 μl aluminium sample pans at a heating rate of 1°C min^{-1} following cooling at 10°C min^{-1} (Reprinted from Thermochim. Acta, 294, C.B. McCrystal, J.L. Ford, and A.R. Rajabi-Siahboomi, A study on the interaction of water and cellulose ethers using differential scanning calorimetry p. 97, Copyright (1997), with permission from Elsevier Science).

the samples. Samples should be re-weighed prior to analysis to confirm that no moisture loss has occurred. In such determinations, the enthalpy of fusion of water should be corrected for sub-ambient temperature ranges, using equations based on the specific heat of supercooled water (Zhang et al., 1989). Joshi and Wilson (1993) demonstrated that the onset temperatures corresponding to bulk water decreased as the proportion of HPMC E5 in the sample increased. The melting endotherms on heating displayed fronting that was attributed to overlapping of endotherms corresponding to Type I and II water. Joshi and Wilson (1993) expressed the amount of water as an R-value, i.e. the number of moles of water added to the polymer, calculated as a polymer repeating unit (PRU). Assuming a molecular weight of 172.26 PRU^{-1}, Joshi and Wilson (1993) showed that for samples with an $R < 4.4$, a melting endotherm was not observed indicating water was tightly bound to HPMC E5. Symmetrical endotherms in similar ethylcellulose–water samples (Joshi and Wilson, 1993; Dabbagh et al., 1996), coupled with a melting point close to that of pure water, indicated a much weaker interaction of water with the hydrophobic ethylcellulose.

In cooling curves, two exothermic peaks of crystallisation of water were observed in hydrophilic polymers (Nakamura et al., 1983). In polyhydroxyethylene derivatives, onset values were −18°C (free water) and −40°C (Type II water). In water–soluble polymer systems, the crystallisation of Type I and II water overlapped in solutions containing hyaluronic acid and its esters (Joshi and Topp, 1992). Indeed, this was apparent in HPMC solutions (Mitchell, 1992; McCrystal, 1998). Aoki et al. (1995) demonstrated a linear relationship between the heats of melting or crystallisation and the water content, expressed as w/w dry polymer for a solid made from hydroxypropylcellulose and ethylcellulose. The amount of non-freezing water in the solid was obtained by extrapolation to the x-intercept. The melting enthalpy of water can be derived from the slope of such plots. Values greater than that of pure water (334 J g^{-1}) were reported and attributed to an interaction between water and the polymeric mixture of hydroxypropylcellulose and ethylcellulose.

In the first paper in a series of studies by Mitchell, Ford and various co-workers, Mitchell et al. (1989) initially examined gels containing HPMC and propranolol hydrochloride using DTA. Two endotherms were noted on heating gels containing up to 40% HPMC K15M. The melting of free ice occurred at 0°C but poorly reproducible endotherms at 5–25°C during heating at 10°C min^{-1}, following rapid cooling to −25°C, were also apparent. Propranolol hydrochloride reduced the enthalpies of these transitions due either to inclusion of water into the drug–water eutectic or to competition for water between the drug and HPMC K15M. A straight line relationship existed between the enthalpies of the transition and the % HPMC polymer in the solutions containing no drug. Extrapolation to zero enthalpy suggested that the minimum ratio of water required to fully hydrate the polymer was 49:51 water/HPMC K15M (w/w). It was suggested that water bound to the HPMC was released by the presence of drug. In these early studies, the scanning rate was 10°C min^{-1} and no transitions were reported to the low temperature side of the melting of ice in the gels. However, Perez-Marcos et al. (1994) reported some low temperature transitions in similar solutions containing carbopol 974.

Ford and Mitchell (1995) explored further the DSC of solutions in the composition range 10–40% w/w HPMC K15M. The solutions were cooled to −30°C, either rapidly or at a rate of −3°C min^{-1} and subsequently heated at 10°C min^{-1}. Irreproducible scans were found after rapid cooling. The melting endotherm at ~0°C was sometimes a combination of two or three endotherms. Another endotherm was apparent between 5 and 25°C. The proportion of these endotherms was cooling rate dependent, the faster the cooling rate, the greater the enthalpy associated with this second endotherm. Slow cooling rates (<5°C min^{-1}) produced only the main endotherm at 0°C (Ford and Mitchell, 1995). The precise nature of the events was not fully explored but the overlapping endotherms may have been due to the development of a metastable, non-equilibrium state formed on cooling and the peaks at >5°C may represent mesomorphic transitions or the production of transient tertiary structures. Doelker (1993) similarly reported liquid crystals in HPMC solutions at room temperature and at 37°C.

The solutions, once cooled, were generally scanned at 10°C min^{-1} (Mitchell et al., 1989; Ford and Mitchell, 1995). Generally single endotherms were reported whose enthalpies decreased with increase in polymer content (Fig. 6). Ford and Mitchell (1995) assumed that these endotherms corresponded to the melting of water that was not bound to the polymer. Their onsets originated at ~−10°C which may due to the melting of small crystallites. Again, a straight line relationship was obtained by plotting the heat of fusion against % HPMC content (Ford and Mitchell, 1995). Extrapolation to zero fusion gave an estimate of the minimum water content as 44% water: 56% HPMC K15M for solutions that were 2 h old. This was calculated as being equivalent to 8.5 mol H_2O PRU^{-1}. After 24 h, the heats of fusion increased in value. The extrapolated ratio became 38:62 water/HPMC K15M (w/w) which is equivalent to 6.6 mol H_2O PRU^{-1}. This value is similar to that obtained by Joshi and Wilson (1993) for HPMC E5 (6.2 ± 1.3 mol PRU^{-1}). The change in values on storage was attributed to syneresis within the gels, liberating free water. The addition of propranolol hydrochloride caused deviation from linearity which was attributed to changes in water distribution. In the presence of this drug, less water was required to fully hydrate the HPMC K15M (Ford and Mitchell, 1995)

Nokhodchi et al. (1997) examined the DSC scans of HPMC/water systems equilibrated for 4 days. Weighed quantities of water and weighed 6.35 mm diameter wafers of HPMC K4M were separately placed into DSC pans which were hermetically sealed and stored at room temperature for 4 days. Samples with a water/HPMC K4M ratio of <0.45 failed to show a melting endotherm at 0°C indicating that there was no free water in the system. At a ratio of ~4.33 the on-set temperature was −2°C and when the ratio was 1.08 the onset was −7.4°C. Two methods were used to quantify the amount of water bound to HPMC, those of Ford and Mitchell (1995) described above and of Sung (1978). The method

of Ford and Mitchell (1995) utilised a plot of fusion enthalpy against % HPMC content. The method of Sung (1978), similar to that described by Joshi and Wilson (1993) produced straight lines when enthalpies (measured as J g^{-1} of dry polymer) of fusion were plotted as a function of grams of water per gram of polymer. A typical plot is given in Fig. 7. Estimates of the amount of water per PRU were six to seven (Sung's method) or five to six (method of Ford and Mitchell), as seen in Table 2. Neither particle size nor viscosity grade appeared to change this value (Nokhodchi et al., 1997).

The purpose of many of these studies was to estimate the amount of free water in the systems, as evidenced by heats of fusion during heating. The enthalpy of the melting endotherm was used to estimate the amount of water not bound to the polymer. At the scanning rates thus far described (10°C min^{-1}) other transitions may be lost. McCrystal et al. (1997a) used a combination of cooling conditions (from rapid to -1°C min^{-1}) and heating conditions (1–100°C min^{-1}) to evaluate their effects on the DSC scans. Mixtures of differing water content were also formed by drying solutions of lower polymer content at 55°C. This is in contrast to earlier studies (Mitchell and co-workers) where the gels were made by heating water, adding and dispersing the polymer and subsequent cooling before adding water to produce the required concentration. McCrystal et al. (1997a) reported that although no pre-endothermic transitions were observed in solutions containing 20% HPMC K15M at a scanning rate of

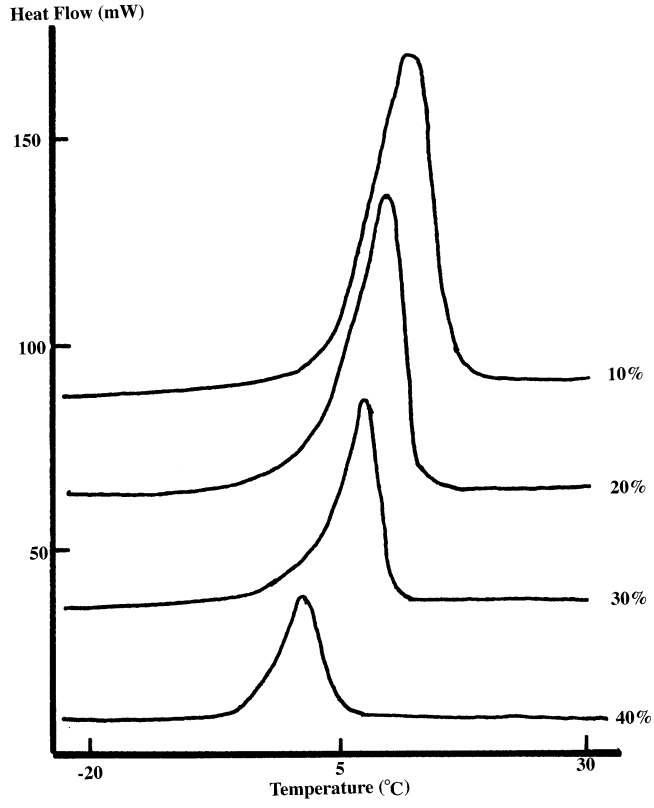

Fig. 6. DSC curves of 2-h-old aqueous gels containing 10, 20, 30 or 40% hydroxypropylmethylcellulose K15M obtained using sealed 40 μl aluminium sample pans at a heating rate of 10°C min^{-1} following cooling at 3°C min^{-1} (Reprinted from Thermochim. Acta, 248, J.L. Ford and K. Mitchell, Thermal analysis of gels and matrix tablets containing cellulose ethers, p. 340, Copyright (1995) with permission from Elsevier Science).

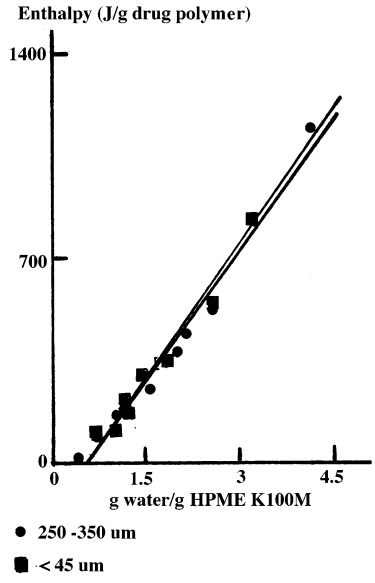

Fig. 7. Enthalpies of fusion (J g^{-1}) of water:hydroxypropylmethylcellulose K100M mixtures prepared by compressing the HPMC into 10 mg discs, placing into DSC sample pans and adding weighed quantities of water. The enthalpies are plotted as a function of grams of water per gram of polymer for two different polymer size fractions (Reprinted from J. Pharm. Sci., 86, A. Nokhodchi, J.L. Ford and M.H. Rubinstein, Studies on the interaction between water and (hydroxypropyl)methylcellulose, p. 610, Copyright (American Chemical Society, 1997), with permission from Elsevier Science).

10°C min^{-1} and stored for 2 h, some events were apparent in solutions stored for 24 h. In contrast to the results of Ford and Mitchell (1995), decreased enthalpies were apparent in gels stored for 24 h. However, the enthalpies increased for solutions subsequently stored for 96 h. Values of moles of water per PRU were ~ 8 and ~ 3.8 for systems stored for 24 and 96 h, respectively, the changes being attributed to syneresis. McCrystal et al. (1997a) concluded that batch to batch variation, the method of gel preparation, and HPMC content contributed to the nature and number of events apparent. Some irreproducible secondary events were apparent in the cooling curves. However, on heating, pre-endothermic events were visible. For instance for gels containing $\sim 30\%$ water, an initial endotherm was clearly seen at a heating rate of 50°C min^{-1} whereas, at 1°C min^{-1}, this endotherm was not as exaggerated but other inflections became more visible. These events probably corresponded to melting–recrystallisation events, although the occurrence of a glass transition can not be overruled (McCrystal, 1998). The occurrence of more than one glass transition has been frequently demonstrated in solutions containing carbohydrates or polysaccharides (Schenz, 1995). For example, Roos and Karel (1991), by careful use of annealing, demonstrated that a Tg′ corresponding to the glass transition of a maximally freeze-concentrated solute exists. It is possible that these low temperature thermal events in HPMC gels may be due to similar phenomena.

Dielectric measurements may not always be suitable for the investigations of water–polymer interactions due to the high dipole moment of water molecules (Hatakeyama and Hatakeyama, 1998). However McCrystal et al. (1998) utilised this process to re-examine the thermal events seen during the DSC of frozen gels (McCrystal et al., 1997a) and confirmed that the presence of drugs could modify these events.

An alternative approach to investigate the interaction of water with cellulose ethers is to examine their heats of solution by calorimetry. Joshi and Wilson (1993) derived a total heat of solution for HPMC E5 of -24.1 cal g^{-1} derived from a net heat of solution (-32.8 cal g^{-1}), a small heat during the glass transition (1 cal g^{-1}) and a value of 7.7 cal g^{-1} for the heat of melting of HPMC. The total heat of solution thus corresponds to a sum of the heats of various processes including hydration, swelling and dispersion. Using partially hydrated samples and solution calorimetry, Joshi and Wilson (1993) also determined that the addition of ~ 5 mol H_2O PRU^{-1} to HPMC E5 resulted in the liberation of 17 cal g^{-1} heat. This was 71% of the total heat derived from the dry sample. Thus the majority of heat evolved on dissolution is due to the addition of tightly bound water to the polymer. Joshi and Wilson (1993) considered that the dissolution of HPMC E5 into water has exothermic and endothermic components. The heat of solution and specific heat capacity values appeared to depend on the addition of tightly bound water.

Table 2
The slopes, intercepts and values of water bound per polymer repeating unit determined using the methods of Sung (1978) or Ford and Mitchell (1995) for different particle sizes and viscosity grades of hydroxypropylmethylcellulose[a]

HPMC	Particle size (μm)	Method of Sung		Method of Ford and Mitchell	
		Slope (J g^{-1})	Water moles bound PRU^{-1}	Intercept (J g^{-1})	Water moles bound PRU^{-1}
K100	<45	321 ± 7	6.1	312 ± 8	5.8
K100	250–350	305 ± 7	6.3	296 ± 7	6.2
K4M	<45	309 ± 12	6.0	277 ± 8	5.0
K4M	250–350	331 ± 10	6.2	326 ± 15	6.1
K15M	<45	305 ± 10	6.7	282 ± 13	5.5
K15M	250–350	322 ± 7	6.1	309 ± 8	5.8
K100M	<45	314 ± 14	6.6	296 ± 16	6.1
K100M	250–350	325 ± 16	7.0	296 ± 15	6.0

[a] (Reprinted from J. Pharm. Sci., 86, A. Nokhodchi, J.L. Ford and M.H. Rubinstein, Studies on the interaction between water and (hydroxypropyl)methylcellulose, p. 611, Copyright (American Chemical Society, 1997), with permission from Elsevier Science).

3.2. Cloud points and thermal gelation

Solutions of methylcellulose and HPMC in water exhibit the phenomenon of thermoreversible gelation. Thus they gel on heating and re-dissolve on cooling (Sarkar, 1995). A summary of these processes is given in Fig. 8. These polymer solutions also show a lower critical solution temperature which may be described as a cloud point. Above this temperature the polymer precipitates. Dehydration to form a precipitate can be monitored turbidimetrically. Solution calorimetry may be used to measure the endothermic heat of dehydration or the exothermic heat of hydration (Sarkar and Walker, 1995). On heating solutions, light transmission–temperature curves can be used to measure characteristics such as the incipient precipitation temperature (IPT) where a sharp decrease in light transmission occurs and the cloud point (CP) which is the temperature where light transmission reaches a 50% value. Similar values can be obtained from cooling curves. Values depend on substitution, molecular weight, molecular weight variation, etc. (Sarkar and Walker, 1995).

Thermal gelation is caused by hydrophobic interactions between molecules containing methoxyl groups. At low temperatures, the cellulose molecules are hydrated and there is little polymer–polymer interaction apart from entanglement. As the temperature rises the solutions become less viscous and their viscosity decreases. Before dehydration is complete, polymer–polymer association occurs leading to an increase in viscosity (Sarkar, 1979). The temperature at which this occurs is called the thermal gelation temperature and is affected by the type of cellulose ether and the presence of ionic materials in solution which may lead to salting out of the polymer. Solutions of HPMC K types gel at 70–90°C, depending on polymer concentration (Sarkar, 1979).

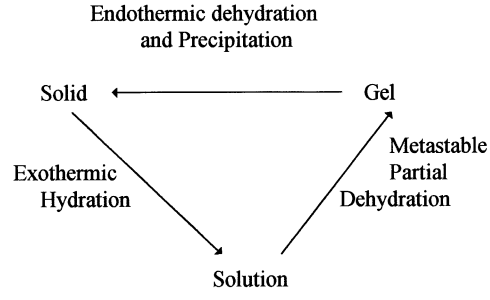

Fig. 8. A summary of the sol–gel transformation of aqueous solution of methylcellulose or hydroxypropylmethylcellulose (Reprinted from Carbohydr. Polym., 26, N. Sarkar and L.C. Walker, Hydration-dehydration properties of methylcellulose and hydroxypropylmethylcellulose in aqueous solutions, pp. 177–185, Copyright (1995), with permission from Elsevier Science).

The cloud point decreases for solutions of methylcelluloses of differing molecular weights up to a polymer content of ~2%, but is thereafter largely unaffected by further increase in concentration. The gelation temperature, however, shows a linear decrease in temperature with increase in polymer concentration. Sarkar (1979) also noted that gelation is a time dependent phenomenon resulting in an increase of gel strength with time. Gel points, incipient precipitation temperatures and cloud points appear to be independent of molecular weight in 2% gels due to the polymer containing high molecular weight fractions. Gel strengths depend on the molecular weight of the cellulose ether. Gelation depends on the degree of total substitution and the degree of hydroxypropyl substitution. The cloud points were 70, 65 and 61°C for 2% aqueous solutions of HPMC K4M, HPMC F4M and HPMC E4M, respectively (Sarkar, 1979). As the hydroxypropyl substitution increases, the gel strength decreases and HPMC K4M gives mushy gels. The addition of solutes, e.g. sodium chloride into the gels, may decrease the incipient precipitation temperature but increase the gel strength (Sarkar, 1979).

The cloud points for 2% w/w solutions were given as 46.0, 56.0, 57.8 and 70.7°C for methylcellulose, HPMC E4M, HPMC F4M and HPMC K4M, respectively (Mitchell et al., 1993a). These variations may be explained by the type and quantity of the substitution groups. The cloud points decreased with increase and concentration and Mitchell et al. (1993a) determined that the concentrations giving cloud points at 37°C were 3, 15, 17 and 22% w/w for methylcellulose, HPMC E4M, HPMC F4M and HPMC K4M, respectively. This low value for methylcellulose was used to explain the poor performance of its matrices in maintaining their integrity on exposure to water.

Sarkar and Walker (1995) investigated the hydration–dehydration properties of solutions of methylcellulose and HPMC. Depending on the temperature and substitution values, cellulose ethers exist in a number of states (Fig. 8). Generally when the cloud points of solutions of cellulose ethers are determined from heating and cooling curves, these is a hysteresis between the values, with the dissolution of the polymer on

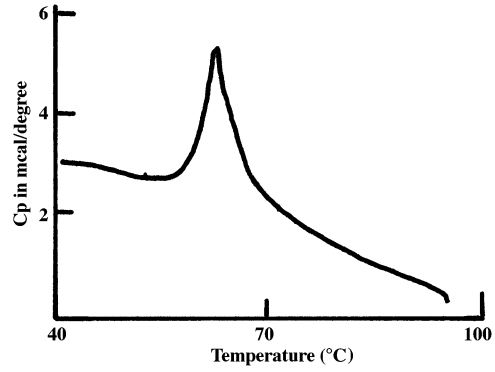

Fig. 9. DSC scan of a 4.67 mg ml^{-1} aqueous solution of a Methocel™ A4M (methylcellulose) sample obtained using a high sensitivity differential scanning microcalorimeter at a scan rate of 1°C min^{-1} (Reprinted from Carbohydr. Polym., 26, N. Sarkar and L.C. Walker, Hydration-dehydration properties of methylcellulose and hydroxypropylmethylcellulose in aqueous solutions, pp. 177–185, Copyright (1995), with permission from Elsevier Science).

cooling occurring at lower temperatures than precipitation on heating. Methylcellulose exhibits a greater hysteresis and lower turbidity than HPMC samples in the determination of cloud points by heating/cooling techniques (Sarkar and Walker, 1995). The curves are dependent on the substitution values of HPMC, are concentration dependent and vary to the storage history (Sarkar and Walker, 1995) but not on heating and cooling rates.

When examining solutions of HPMC or methylcellulose by high sensitivity DSC (model MC-2D, Microcal Instruments) to determine the endothermic heat of dehydration (Sarkar and Walker, 1995), careful degassing of the samples was required and slow scanning rates (1°C min^{-1}) were used to record specific heat data. The cell size was 1.2 ml. Such plots showed that the dehydration of methylcellulose (all solutions used were 0.5%) followed a single precipitation process with a two state sol–gel transition (Fig. 9). HPMC samples were more complicated. For example, HPMC K4M demonstrated a broad endotherm centred at 75°C with a small transition at 81°C, possibly suggesting a phase transition (Sarkar and Walker, 1995). The order of the enthalpies of dehydration were HPMC K4M < HPMC F4M <

Methylcellulose A4M < HPMC E4M; the energy for HPMC E4M being approximately three-times that of HPMC K4M. Values were 0.758, 1.043, 0.734 and 0.366 kcal PRU^{-1} for methylcellulose A4M, HPMC E4M, HPMC F4M and HPMC K4M, respectively. A possible correlation was shown between the heat of dehydration with the combined value of DS (degree of methoxyl-substitution) and MS (molar substitution). This indicated an increased water structure breakage around the polymer due to hydrophobic bonding with increased total degree of substitution. HPMC K4M had the lowest total degree of substitution and the lowest heat of hydration (Sarkar and Walker, 1995).

Mitchell et al. (1990) used cloud points to examine the interaction between drugs and excipients on solutions of HPMC K100 or HPMC K15M. Changes in pH, from 3 to 12.3, did not effect the cloud points of 2% HPMC K100 solutions (68.8–70.4°C), but at pH 1 a value of 64.5°C was obtained compared with 70.4°C for unbuffered solutions containing 2% HPMC K100. Inorganic salts reduced the cloud point according to the position of the ions in the lyotropic series, the order being chloride < tartrate < phosphates and potassium < sodium (Mitchell et al., 1990). Anions were more important than cations in lowering the cloud point. A consequence of these effects was that as the ionic strength increased, the dissolution rates decreased to a minimum before rising to give a 'burst' release. Disintegration times of HPMC tablets, without active, also varied to the ionic strength of the disintegration medium. It proved possible by determining the cloud points to predict if a matrix would show burst release in a given electrolyte solution. Of several drugs examined, propranolol hydrochloride, promethazine hydrochloride, aminophylline and tetracycline hydrochloride increased the cloud points while theophylline and quinine bisulphate had little effect (Mitchell et al., 1990). Importantly, since a reduction in cloud points is an indication of decreased solubility of the polymer and therefore an indication of a decreased ability to imbibe water, cloud points were used as an indication of an inability of HPMC to hydrate on exposure to fluids and of failure to form a protective gel around the surface of tablets. (Mitchell et al., 1990). The increase in cloud points (Mitchell et al., 1990) and alteration to melting endotherms seen in HPMC solutions containing propranolol hydrochloride (Mitchell et al., 1989) were put forward as indicators that HPMC and drugs complete for water in matrices. Clearly if both the drug and the buffer surrounding the matrix during dissolution tests salt out the cellulose ether, there is the possibility of burst release of a drug. For example, matrices containing diclofenac sodium tested in phosphate buffer, disintegrated (Rajabi-Siahboomi, 1993).

Sarkar (1995) used oscillatory shear measurements to characterise solutions containing methylcellulose or HPMC and to examine the kinetics of gelation by comparing values of storage modulus (G') and loss modulus (G''). The influences of temperature on G' and G'' were used to study gelation. G' values exhibited a minimum where gelation took place for methylcellulose solutions (Fig. 10). The gelation behaviour of HPMC is considerably different (Sarkar, 1979) and depends on molar substitution of the hydroxypropyl groups (MS). HPMC solutions exhibited two infl-

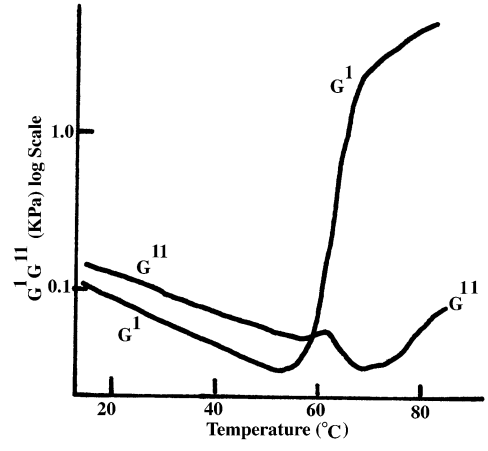

Fig. 10. The influence of temperature on the G' and G'' values for a 2% solution of a 4000 mPa viscosity grade methylcellulose at a frequency of 10 Hz and 10% amplitude heated at a scan rate of 1°C min^{-1} (Reprinted from Carbohydr. Polym., 26, N. Sarkar, Kinetics of thermal gelation of methylcellulose and hydroxypropylmethylcellulose in aqueous solutions, pp. 195–203, Copyright (1995), with permission from Elsevier Science).

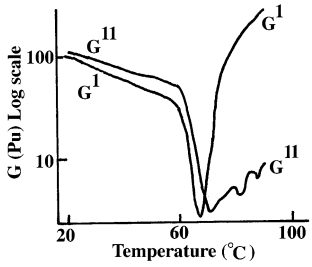

Fig. 11. The influence of temperature on the G' and G'' values for a 4% solution of a 4000 mPa viscosity grade hydroxypropylmethylcellulose polymer with DS of 1.85 and MS of 0.16 at a frequency of 1 Hz and 8.5% amplitude heated at a scan rate of 1°C min^{-1} (Reprinted from Carbohydr. Polym., 26, N. Sarkar, Kinetics of thermal gelation of methylcellulose and hydroxypropylmethylcellulose in aqueous solutions, pp. 195–203, Copyright (1995), with permission from Elsevier Science).

ection points (Fig. 11). On increase of temperature, the G' and G'' values were lowered until a temperature was reached where the values decreased sharply (Sarkar, 1995). On further increase in temperature the solutions began to gel and both G' and G'' values increased, the G' values increasing sharply. The gel strengths of HPMC solutions increased with increase in DS and decreases in MS.

The thermogelation of methylcellulose and HPMC was measured thoroughly by Haque and Morris (1993) and Haque et al. (1993), when the effects of increased temperature on the cellulose structure were examined. Haque and Morris (1993) examined the thermodynamics of the interaction between water and methylcellulose. A Setaram microcalorimeter was used to examine solutions of methylcellulose at a heating and cooling rate of 0.1° min^{-1}. Rheometric studies suggested that there were two regions of change in the storage moduli (G') on both heating and cooling. DSC, on a solution of 2% methylcellulose showed a single endotherm on heating which began towards the end of the first wave of increase in G' but two exotherms on cooling which corresponded to the two regions of reduction in G'. The energy of the transition, derived from heating and cooling curves, was 16 ± 1 J g^{-1}. The structuring processes were reversible on cooling but offset to lower temperatures. The interpretation provided by Haque and Morris (1993) was that methylcellulose chains exist in solution as aggregated bundles held together by packing of un-substituted or sparingly soluble regions of the cellulosic structure and by hydrophobic clustering of methyl groups in regions of denser substitution. On increase in temperature these bundles come apart exposing methyl groups to the aqueous surroundings and causing a large increase in volume. At higher temperatures the methyl substituents lose structured water and form a hydrophobically cross-linked network (Haque and Morris, 1993).

The thermogelation of HPMC E4M HPMC K4M and HPMC F4M followed a two stage process involving dissociation of cellulose 'bundles' as a precursor to hydrophobic association (Haque et al., 1993). Sharp cooling exotherms and heating endotherms were observed for hydroxypropylcellulose gels corresponding to mixing and de-mixing. Limiting values for these heats of transition by extrapolation or otherwise were in the range 27–30 J g^{-1} (Robitaille et al., 1991; Haque et al., 1993). Haque et al. (1993) used a very slow rate (0.1°C min^{-1}) to examine the DSC of solutions containing HPMC E4M, HPMC F4M and HPMC K4M. Each sample gave a single endotherm on heating and a single exotherm on cooling (Haque and Morris, 1993) compared with methylcellulose A4M which gave a single endotherm on heating whereas on cooling a double exotherm was obtained (Haque et al., 1993). These temperatures correlated with the rheological properties of the materials. The cooling exotherm was postulated to be due to the formation of water cages around the hydrophobic constituents exposed to the aqueous environment. The extra exotherm for A4M was ascribed to enthalpic interactions with cellulose bridges and was not observed for HPMC products implying that the hydroxypropyl substituents caused a reduction in the stability of the bonds. Enthalpies, averaged for values determined for solutions containing 0.5, 1 or 2% polymer and at rates from 0.1 to 0.5°C min^{-1} were determined as 15.9 ± 0.5, 4.6 ± 0.3, 15.3 ± 0.5, 4.2 ± 0.2 J g^{-1} (polymer) for methylcellulose A4M, HPMC E4M, HPMC F4M and HPMC K4M, respectively. The low value for

HPMC K4M was attributed to its lower degree of substitution and therefore a reduction in the stability of water around the polymer chains. Optical rotation and nuclear magnetic resonance were used to confirm findings. Hysteresis was observed between the formation and dissociation of HPMC and methylcellulose gels arose from melting and reformation of structure and not from hydrophobic interactions (Haque et al., 1993).

The enthalpy of transitions of the gel–sol gel transitions is very small and hence highly sensitive measurements are thought to be needed to determine the enthalpies of these transitions. However, unpublished data (Ford, 1998) showed that in large volume stainless steel pans and a fast heating rate (10°C min^{-1}), transitions could be detected from 2% solutions of methylcellulose, although a second endotherm was seen at ~90°C (Fig. 12). The enthalpy of the first transition was 0.251 J g^{-1} (solution) or 12.6 J g^{-1} (polymer), a value similar to that obtained by Haque et al. (1993).

4. Rates of hydration and water uptakes

Obviously the speed of the initial water uptake and of the conversion to a viscous layer are important criteria in the control and mechanisms of drug release from matrices. It has been suggested that the substitution type of HPMC will enable the release rate of drugs to be modified (Alderman, 1984). Rapid hydration to form the protective 'gel layer' is required to prevent water soluble components from rapidly dissolving. HPMC K types are considered to hydrate faster than E, F or A types of methocels, the order being HPMC K > HPMC E > HPMC F > methylcellulose A (Doelker, 1987).The substitution type and the solubility of the drug should be considered when formulating hydrophilic matrices (Alderman, 1984).

The rates of hydration for the polymers have been determined by solution calorimetry. In a method described by Sarkar and Walker (1995), a compressed 250 mg tablet of the cellulose ether was placed in a solution calorimeter at 37°C to make a final concentration of 1%. The exothermic heat of solution was measured as a function of time. Its values were HPMC E4M > HPMC K4M > HPMC F4M > methylcellulose A4M. The data did not, however, reflect the process rates since the number of moles of polymer were not

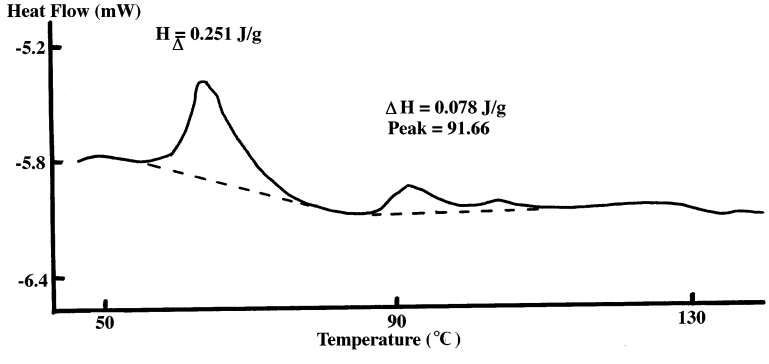

Fig. 12. DSC curve of an aqueous solution containing 2% methylcellulose A4M obtained using large volume stainless steel capsules, ~65 mg sample, at a heating rate of 10°C min^{-1}.

determined. Therefore the data were normalised by dividing the exothermic heats by the heats of dehydration obtained by DSC (Sarkar and Walker, 1995). The ranking then became HPMC K4M > HPMC F4M > HPMC E4M > methylcellulose A4M.

However studies examining the water uptake of methylcellulose A4M, HPMC E4M, HPMC F4M and HPMC K4M indicate that the uptake may not be significantly different and that other factors accounting for the differences in release rates should be sought (Mitchell et al., 1993a). Mitchell et al. (1993a) demonstrated that the release rates of propranolol hydrochloride from matrices containing methylcellulose or HPMC was independent of the substitution type in matrices containing 75–150 mg polymer.

DSC was used to assess this initial inclusion of water into a gel-forming matrix (Mitchell et al., 1993a). For each run, a quantity of water, approximately 10 mg, was accurately weighed into a traditional Perkin-Elmer DSC flat sample pan and covered with a wafer of the polymer (6.35 mm diameter and prepared by compression) and a lid. Following timed storage at ambient or 37°C, the sample was re-weighed and cooled to −30°C at 200°C min^{-1}. and then scanned at 10°C min^{-1} to examine the melting process of the water. The enthalpy of the melting process was compared with the value anticipated from the weight of water included in the pan and the weight of water bound to the polymer calculated. Peak shape gave an indication of the complexity of the binding of water to the polymer. Broad endotherms, commencing in the range −10 to −20°C were observed for HPMC and methylcellulose (Mitchell et al., 1993a). No differences were found in the water uptake of HPMC E4M, HPMC F4M or HPMC K4M or methylcellulose A4M, despite claims in the literature that these materials hydrate at different rates according to their degrees of substitution (Mitchell et al., 1993a). During the initial 5 min of exposure to water, 30% of the water uptake occurred. Peak broadening was not apparent in the DSC scans of similar discs containing the hydrophobic ethylcellulose, indicating a probable lack of bound freezable water (Dabbagh et al., 1996). Additionally, in the time scale of the studies (30 min) uptake by ethylcellulose was only ~20% that of a HPMC K4M system.

Although the substitution type may effect the release of soluble drugs, for less soluble drugs polymers hydrating more slowly are preferred in order to limit the gel layer growth (Doelker, 1987). Once the 'gel layer' has formed its properties such as gel strength (Wan et al., 1992), its growth rate (Colombo et al., 1987b) and water/drug diffusivity within the gel control the release.

Coarse fractions of HPMC are thought to hydrate too slowly to allow sustained release (Alderman, 1984). Tablets made from coarse particle size fractions may disintegrate before hydration occurs to form a 'gel layer' around the matrix which protects the internal drug from dissolution (Mitchell et al., 1993c). Small fractions allow uniform hydration into the matrix, thereby retarding release. DSC of water uptake into wafers displayed that uptake by a >355 μm fraction) was faster than by a <75 μm fraction of HPMC K15M (Mitchell et al., 1993c). Similarly a <45 μm fraction of HPMC K4M imbibed water more slowly than a 250–350 μm fraction (Nokhodchi et al., 1997). The onset temperature corresponding to the melting of ice concomitantly decreased from −2.3 to −7.2°C as the disks were held in contact for water for 1 and 30 min, respectively.

Although no other transitions were reported for disks of HPMC in contact with water, Perez-Marcos et al. (1994) showed some low temperature transitions to the low temperature side of the melting endotherm for discs containing carbopol 974 or 1:1 carbopol 974:HPMC K4M, indicative of more than one type of water being present. Water uptake ranked as HPMC > 1:1 mixture > carbopol. The technique has also been employed to examine water uptake by discs containing ethylcellulose, HPMC K4M and their 1:1 blends (Dabbagh et al., 1996). Ethylcellulose took up far less water than HPMC over the 30 min contact period. The 1:1 blends took up intermediate levels after 5 min. The melting endotherm of water in contact with ethylcellulose was much sharper than that in contact with HPMC confirming less interaction between water with ethylcellulose than HPMC.

Alternative methods of examining water uptake include dynamic vapour sorption studies (McCrystal et al., 1997b). The molecular weight of HPMC K grades appeared to have little effect on the moisture sorption/desorption characteristics but this behaviour was influenced by the substitution level. HPMC K4M sorbed more water at all RH values compared to HPMC E4M, HPMC F4M and Methylcellulose A4M.

5. Tablet swelling

The relaxation and swelling characteristics of HPMC matrices may influence drug release kinetics (Korsmeyer and Peppas, 1983). These matrices have been shown to expand predominantly in an axial direction (Colombo et al., 1990; Mitchell et al., 1991). This was attributed to an equal contribution of gel growth and of core expansion in this direction (Rajabi-Siahboomi et al., 1994) when NMR-imaging was used to study the dimensional changes in the gel layer and the core of HPMC tablets undergoing hydration. The axial expansion of the core was postulated to be due to uni-axial stress relaxation of compression forces in the core as the hydration proceeded. The overall axial swelling of HPMC E4M tablets was less than HPMC F4M or HPMC K4M grades due to a smaller expansion of the HPMC E4M core (Rajabi-Siahboomi et al., 1994).

Drug release from swelling matrices is dependent on the diffusion and relaxation behaviour of the dosage form (Lee, 1985). The diffusional release is by molecular diffusion down a chemical potential gradient whereas the relaxational release is by drug transport mechanisms associated with the stresses and state transitions involved in the swelling of the hydrophilic polymer. The swelling of the polymer would alter the drug concentration gradient in the gel layer (Colombo et al., 1987a; Conte et al., 1988).

Several methods have been used to assess the swelling of polymers. These include videomicroscopy (Colombo et al., 1990; Wan and Prasad, 1990a,b) and laser methods (Mitchell et al., 1993a). Mitchell et al. (1991, 1993a) also used isothermal thermal mechanical analysis to study the expansion of matrices. Mini-tablets (25 mg polymer; 3 mm flat faced) were prepared and the extension probe of the TMA was placed, under zero pressure, onto the tablet surrounded by water. The axial and radial dimensions were measured. Methylcellulose tablets initially expanded rapidly but disintegrated after about 10–20 min exposure to water (Mitchell et al., 1993a). The swelling for the HPMCs was greater in the axial direction than in the radial direction. The ranking for swelling was HPMC F4M > HPMC K4M > HPMC E4M, the later subsequently shown to be due to a smaller expansion of the un-wetted core (Rajabi-Siahboomi et al., 1994).

Swelling of tablets, followed isothermally in water, showed that drugs could also play an important role in polymer swelling and contribute to matrix integrity. The ability of the drugs to maintain this integrity ranked as propranolol hydrochloride > tetracycline hydrochloride > indomethacin (Mitchell et al., 1991), a ranking that mirrored their ability to salt HPMC into aqueous solution (Mitchell et al., 1990).

The inclusion of drugs may further modify the performance of the swelling of matrices. The soluble drugs tetracycline hydrochloride and propranolol hydrochloride each increase the cloud point of HPMC. Whereas matrices containing only methylcellulose swelled rapidly and disintegrated at 37°C, the inclusion of propranolol hydrochloride, and to a less extent tetracycline hydrochloride prevented this disintegration (Mitchell et al., 1993b), indirect evidence that these drugs modify the water interaction with HPMC and methylcellulose. In the presence of propranolol hydrochloride the ranking of swelling was methylcellulose A4M > HPMC K4M > HPMC F4M > HPMC E4M. For tetracycline this was methylcellulose A4M > HPMC F4M > HPMC E4M ≅ HPMC K4M and in the presence of indomethacin was methylcellulose A4M > HPMC K4M > HPMC E4M ≅ HPMC F4M. The ranking of matrices for HPMC K4M were HPMC K4M > 1:1 tetracycline:HPMC K4M > 1:1 propranolol:HPMC K4M > 1:1 indomethacin:HPMC K4M (Mitchell et al., 1993b).

TMA, in penetration mode, was also used to monitor gel layer formation and Mitchell et al. (1993a) showed that the E4M, F4M and K4M grades of HPMC performed similarly. This layer was assessed from the solvent front (i.e. the edge of the hydrating matrix determined by static probe) and the rubbery–glass interface determined in penetration mode by an elongated probe (Mitchell et al., 1993b). The incorporation of drugs in to the matrices reduced the thickness of the gel layer. In the presence of drugs this layer thickened rapidly following the first h of contact with water but in the absence of drugs the thickness increased for ~ 4 h.

Sophisticated studies such as NMR imaging (Rajabi-Siahboomi et al., 1996) have been used to assess the differences in behaviour of various HPMCs in hydrophilic matrices. Self diffusion coefficients (SDCs) indicated that the middle and inner regions of the gels surrounding HPMC E4M or HPMC K4M were similar but the values for HPMC K4M were lower. SDCs also showed that for HPMC matrices, water in the radial direction was less bound within gels than in the axial direction. This can not be demonstrated by thermal analytical studies.

6. Conclusions

Thermal analysis provides a series of techniques that may be used to assess the interactions of water with HPMC. However, important factors such as particle morphology and shape, particle size distribution and lot to lot variations can not be assessed easily by thermal analytical methods and these contribute to the performance of hydrophilic matrices based on cellulose ethers (Bonferoni et al., 1996). Similarly HPMC viscosity grade is an important factor in the control of release for poorly soluble drugs partly because of the role that erosion plays in promoting drug release for these drugs (Ford et al., 1985). At present only dynamic methods of thermal mechanical analysis may predict this erodability. Interested readers are recommended to the studies of Bonferoni et al. (1992, 1995) for the use of rheological techniques to characterise cellulose ether gels and to relate the disentanglement of HPMC to erosion.

In summary, thermal analysis has been used in a number of disparate studies to study HPMC and methylcellulose systems. Particularly important are the studies that relate changes induced by moisture. However it should be remembered that the method of preparation, for example freezing may result in incomplete crystallisation, and scanning, for example moisture loss during heating, may produce a system different to the starting material. However, thermal analysis is its various guises, is not an invasive technique but the nature of the events seen must be substantiated by other non-thermal techniques. Not withstanding these problems, because of the considerable variability in the polymer and differences in substitution and molecular weight, there is still tremendous scope for the assessment of the physical performances of these cellulose ethers by thermal analysis.

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