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Thermal analysis of gels and matrix tablets containing cellulose ethers

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Abstract

This paper reviews the use of thermal analysis in probing the performance of hydrophilic matrices. Thermomechanical analysis, in isothermal mode, can monitor the rate of gel formation around matrix tablets following their exposure to water; in expansion mode the technique can follow the swelling of matrices exposed to water. DSC can follow the moisture uptake by matrices containing hydrophilic polymers, such as cellulose ethers. In new data, DSC and DTA have been used to assess the water content of gels containing hydroxypropylmethylcellulose (HPMC). The techniques showed that gel syneresis occurred on storage, liberating free water, and that the inclusion of a model drug (propranolol hydrochloride) redistributed the water contained within the gel. Following storage for 24 h, DSC showed that each polymer repeating unit of HPMC was associated with 6.5 moles of water.

Keywords: Cellulose ether; Drug; DSC; DTA; Gel; Matrix

1. Introduction

The states of water in different polymers have been studied by many authors [1–11]. The water structure within gels has been described in terms of thermodynamic states of water, each class having a different physical property, e.g. melting point. Taniguchi and Horigome [11] described four different classes of water contained in cellulose acetate membranes, the classes being completely free water, free water interacting weakly with the polymer, bound water which can contain

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salts and bound water which rejects salts. Bound water can be defined as water that is incapable of freezing at 0°C because of interactions with the polymer. However, the majority of authors [4–6,9,10,12] described models of gel structure which displayed three different states of water. These are generally bound water, free (unbound) water and a weakly bound, interfacial water. However, Roorda et al. [7,8] showed that there was little indication to suspect any kind of water within polyhydroxyethylmethacrylate (p(HEMA)) gels other than free water and bound water. All the authors agreed that bulk water makes up a significant amount of the water content in gels.

Methods that have been used to measure the different states of water include differential scanning calorimetry (DSC) [2,6–8,12], nuclear magnetic resonance (NMR) [13], solute exclusion [14], thermogravimetric analysis [15] and dilatometry [5]. Because each method measures a different physical property of the polymer there can be a large variation in the results obtained by the different methods.

2. Cellulose ethers in matrix tablets

Cellulose ethers, especially hydroxypropylmethylcellulose (HPMC) and methylcellulose (MC) are commonly used in matrix tablets to provide a sustained drug release. Either polymer, when used in matrices which are intended not to disintegrate, hydrates on contact with water to form a gel layer which allows the polymer to be used to facilitate the sustained release of drugs. The release of drugs from HPMC matrices has been well described and effects such as the viscosity grade of HPMC [16–19], temperature [20,21], drug solubility [18,19] and HPMC:drug ratio [16–19] have been characterised. Retardation of drug release is accomplished via the production of a gel layer around the matrix when placed in contact with water [22]. Initially, the cellulose ether swells and the matrix thickness increases. The polymer begins to dissolve in the solvent due to chain disentanglement leading to a slow erosion of the gel. The release of water soluble drugs is predominantly controlled by diffusion of the drug through the gel; insoluble drugs are released by erosion of the gel to expose fresh surfaces containing undissolved drugs.

This paper reviews the use of thermal analysis in characterising drug release from matrices containing cellulose ethers. Provisional findings into the use of thermal analysis in characterising the hydration of HPMC gels [23], the uptake of water into different substitution types of cellulose ethers [24] and the use of thermomechanical analysis to account for the swelling of HPMC matrices [25] have been published. This paper reviews the more recent publications in this field and then presents new data which examine the water equilibrium in HPMC gels, in the absence and presence of a model drug, propranolol hydrochloride. In this study, both differential thermal analysis (DTA) and DSC were used to measure bound and free water in HPMC gels. Thermal analysis has various advantages over other methods, e.g. the ability to rapidly and quantitatively evaluate the water content of a small sample. The use of thermal analysis in analysing polymers has been reviewed [26,27] and more extensively by Ford and Timmins [28]. Additionally the effect of ageing on the water distribution of the gels is examined.

3. Review of the use of thermal analysis in evaluating the performance of matrices containing cellulose ethers

Generally, thermal analysis has been used in three modes to evaluate the performance of matrices, namely water uptake, expansion and estimation of thickness of the gel layer generated once the cellulose ether matrix is placed in contact with water. The latter two measurements utilised isothermal mechanical analysis with the matrices in contact with distilled water.

Water uptake studies were utilised to estimate if the substitution type of the cellulose ether controlled the imbibing of water by the polymers because the literature [22] suggested that alleged different hydration rates of differing substitution types of the cellulose ethers controlled drug release.

Mitchell et al. [29] used DSC to elucidate supposed differences in water uptake by four grades of cellulose ether, commercially available as Methocel A4M, Methocel E4M, Methocel F4M and Methocel K4M, each manufactured by Dow Chemicals, USA, and equivalent to USP types methylcellulose, hydroxypropylmethylcellulose (HPMC) 2910, HPMC 2906 and HPMC 2208.

For measurements, 10 mg samples of the polymers were compressed into wafers of 6.35 mm diameter. The wafers were placed onto 10 mg samples of double distilled water previously weighed into aluminium DSC sample pans. Samples were held at room temperature for up to 60 min prior to the pans and their contents being placed into the sample compartment of a Perkin-Elmer DSC-7 differential scanning calorimeter at -30°C to freeze any unbound water. Samples were scanned at 10°C min^{-1} and the enthalpy of fusion of unbound ice measured. This corresponded to the quantity of water which had not been bound to the cellulose ether.

Typical data are shown in Fig. 1. The onset temperatures decreased from -10 to -17°C as the sample time increased from 30 s to 30 min. Fig. 2, showing data for three HPMCs and methylcellulose, reveals that the water uptakes for all four samples were similar with over 30% of the uptake occurring in the initial 5 min of contact. The data contradict the concept of Alderman [22] that the different substitution grades should hydrate at different rates and partly explain the similarity in release from matrices containing the four grades of Methocel [29]. Interestingly, similar studies on HPMC K15M, a grade of high viscosity, indicated that larger sized fractions of HPMC (>355 μm) hydrated more rapidly than a smaller fraction (<75 μm) [30]. Again this is contrary to the supposition of Alderman [22] that coarser fractions hydrate more slowly than fine granules and therefore result in disintegration of the matrix. After 60 min, however, the two samples imbibed the same quantity of water. However, the first few minutes of hydration are the most important because this period corresponds to the time when the protective gel coat is formed around matrices containing HPMC. The data of Mitchell et al. [30] suggested that coarse particles absorbed 40% more water than the finer particles in the initial 5 min period of contact with water, contrary to the theory proposed by Alderman [22]. Thermal analysis therefore showed that, whatever the reason, it was not due to differences in hydration rate which produced the differences in release

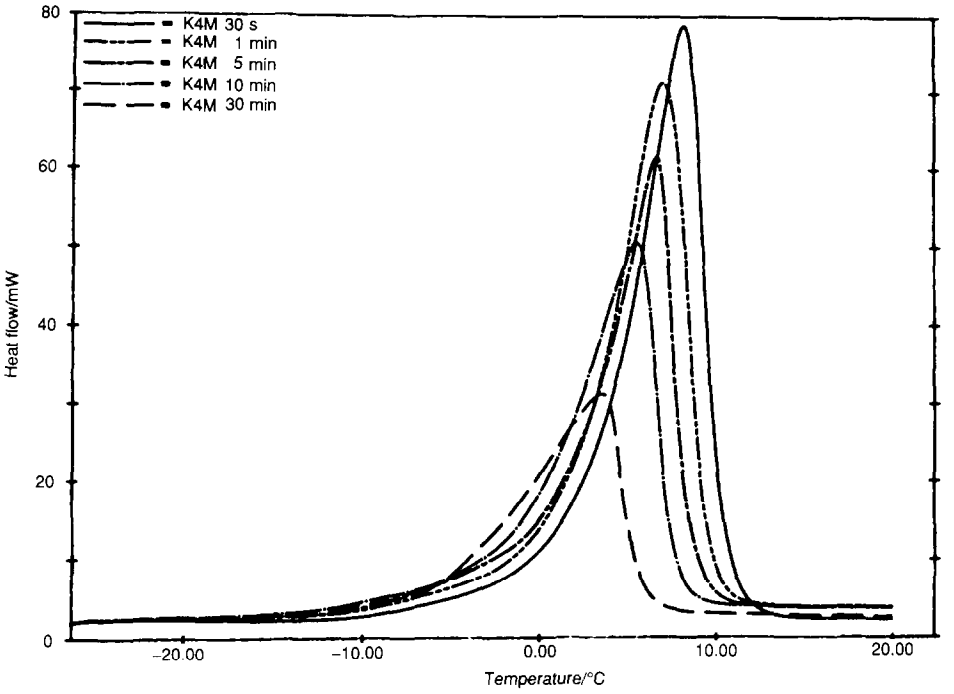

Fig. 1. DSC scans showing the melting endotherms of free water in contact with hydroxypropylmethylcellulose K4M discs from 30 s to 30 min (taken from Ref. [29]).

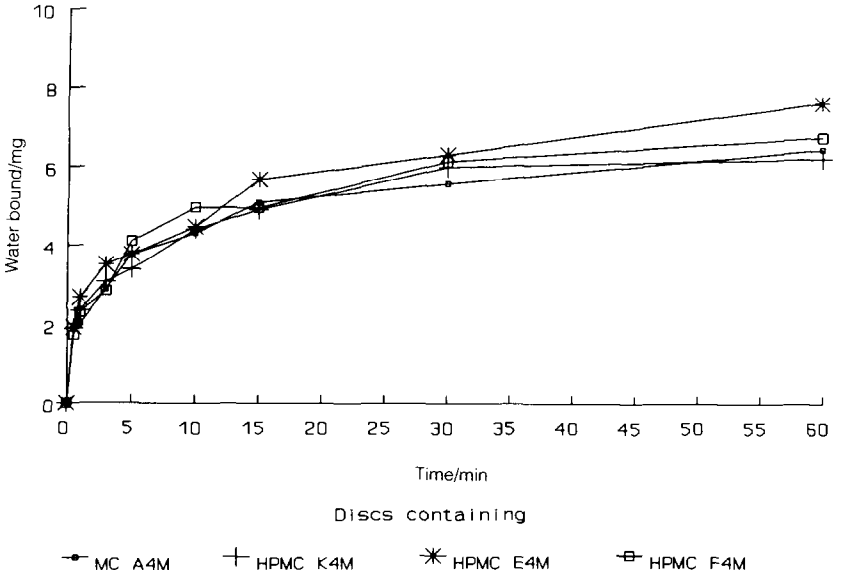

Fig. 2. The effect of time on the water bound by discs of hydroxypropylmethylcellulose K4M (+), E4M (*), F4M (□) or methylcellulose A4M (○) over a period of 60 min (taken from Ref. [29]).

rates claimed for HPMC of different particle size or for cellulose ethers of different substitution type.

Thermal analysis was therefore used to examine the swelling of matrices in water and the rate of gel layer formation. Consequently isothermal thermomechanical analysis was used, exposing matrices to dissolution fluids. Matrix tablets containing only cellulose ether, lubricant [29] or 50:50 cellulose ether and drug were prepared [31]. The sample arrangement is indicated in Fig. 3. The matrix under test was placed in a 100 ml beaker in a water bath, generally maintained at 37°C. The expansion probe was placed on the tablet and water introduced into the beaker at the required temperature. The axial and radial dimensions of the tablets were measured to ± 0.001 cm using a Perkin-Elmer Series 7 thermal mechanical analyser (in expansion mode) controlled by a Perkin-Elmer TAC7 and consequently tablet swelling was assessed [29]. To assess the rate of formation of the gel layer the same apparatus set-up as Fig. 3 was used but the TMA was used in penetration mode using a specially modified probe (1 mm wide; point 1.5 cm long). At hourly intervals the thickness of the gel layer was determined by allowing the probe to sink into the gel with a force of 1000 mN [29].

In the swelling studies, and in the absence of drug [29] methylcellulose A4M matrices disintegrated following around 20 min exposure to water and rapid swelling during this period. For matrices containing methylcellulose A4M, HPMC E4M, HPMC F4M and HPMC K4M swelling in the axial direction was much greater than the radial swelling, as evidenced in Fig. 4. Other studies have shown, using other

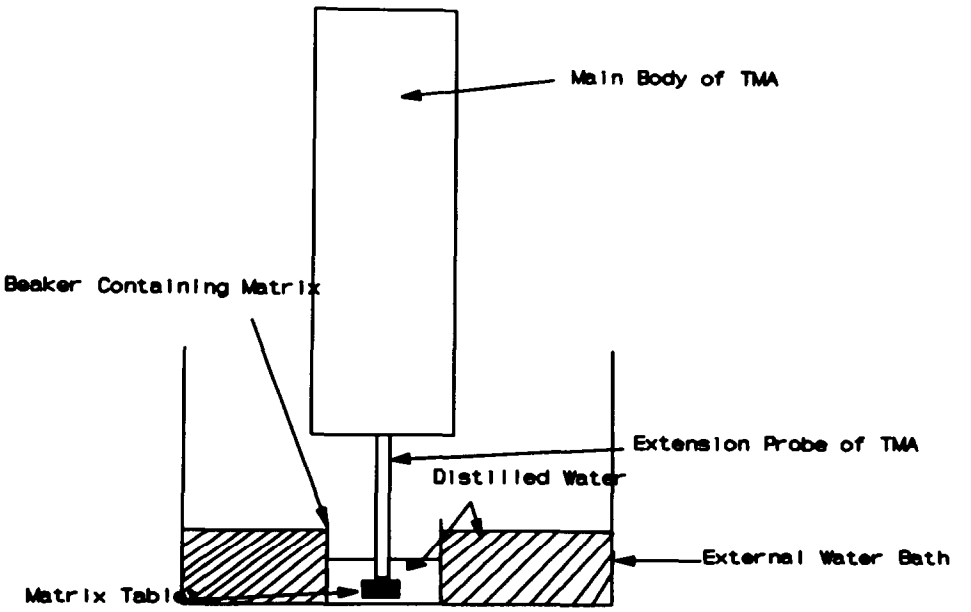

Fig. 3. The thermal mechanical analyser as used to measure the rate and extent of swelling of cellulose ether matrix tablets (taken from Ref. [29]).

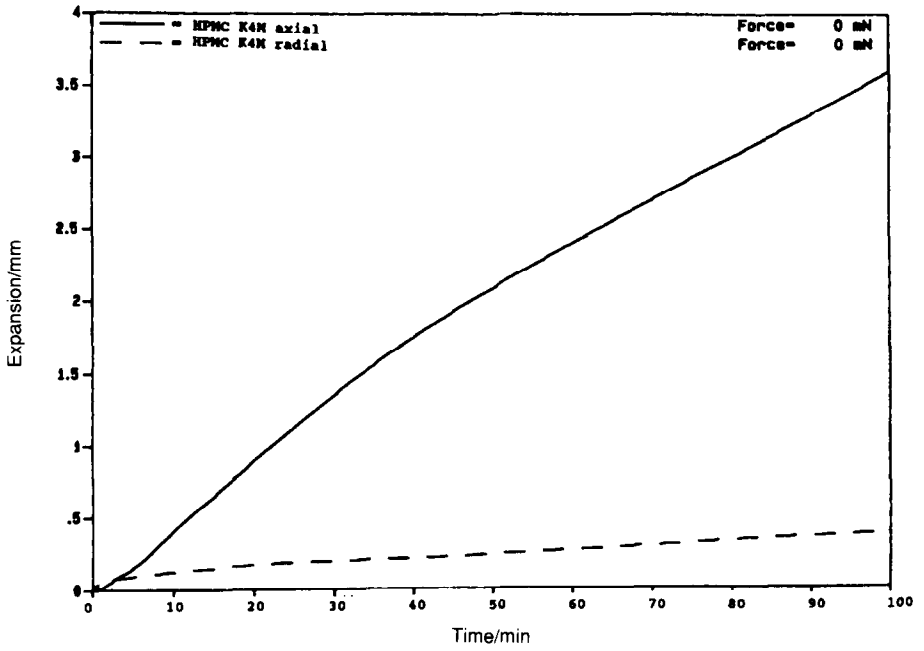

Fig. 4. The axial and radial expansion measured by thermal mechanical analysis of a compact containing hydroxypropylmethylcellulose K4M at a temperature of 37°C (taken from Ref. [29]).

methods of analysis, that axial swelling is greater than radial swelling [32,33]. The extent of swelling ranked as methylcellulose A4M > HPMC F4M > HPMC K4M > HPMC E4M.

Interestingly, when three temperatures (24, 37 and 45°C) were used, it was apparent that the initial 15 min period of swelling was important in determining the extent of swelling; after this time the rates of axial swelling of the matrices were similar. Compacts containing HPMC E4M were least affected by temperature. Methylcellulose matrices swelled at 24°C and did not disintegrate [29]. The explanation for this latter phenomenon was that the cloud points (and hence solubility) of methylcellulose gels were lower than the HPMCs and at 37°C and 45°C this lower solubility caused a failure in the gelation process [29].

The incorporation of 50% drug into the matrices could have a profound effect on the swelling process. For example, propranolol hydrochloride (Fig. 5) allowed matrices containing methylcellulose A4M to swell for the whole of the test period [31] rather than disintegrate in the absence of drug [29]. Possible explanations are that propranolol hydrochloride salted in methylcellulose by increasing its cloud point and hence its solubility. The extent of swelling of the methylcellulose drug matrices was greater than for the HPMC–drug matrices (Fig. 5). Tetracycline had a less profound effect than propranolol [31] and the insoluble drug indomethacin had very little influence on the swelling of the matrices containing cellulose ethers, its only effects being caused by dilution of the polymer [31].

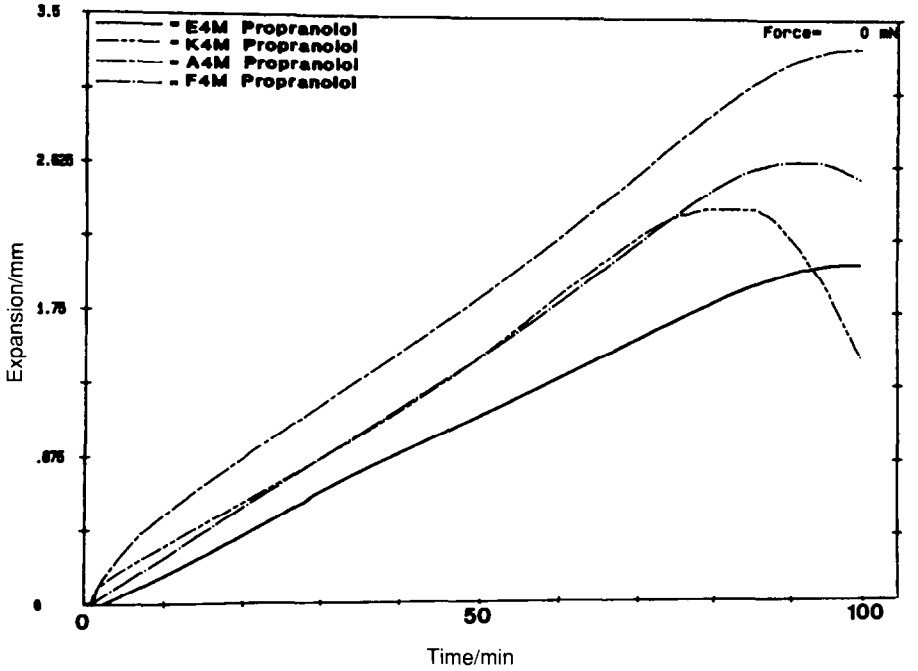

Fig. 5. The axial swelling profiles of matrices containing 50% hydroxypropylmethylcellulose K4M, E4M, F4M or methylcellulose A4M and 50% propranolol hydrochloride at 37°C (taken from Ref. [31]).

Gel layer thickness is important in controlling drug release from matrix tablets, because drug release usually is controlled at least partly by diffusion. Fig. 6, which shows the gel layer thickness generated at 37°C in matrices containing solely

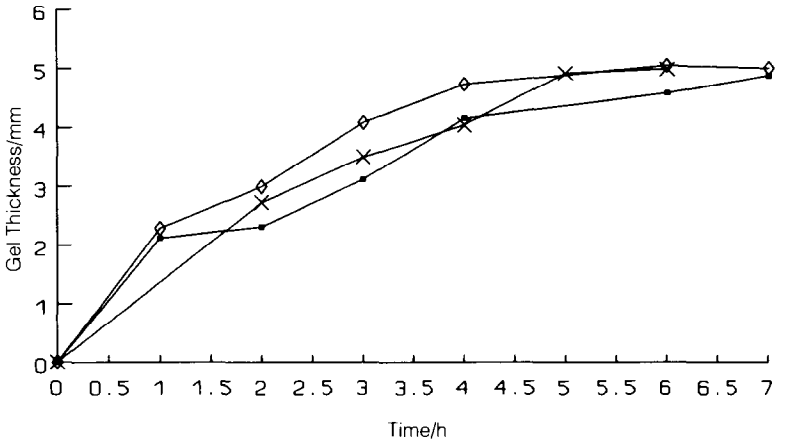

Fig. 6. The effect of time on the gel layer thickness of hydrating matrices containing hydroxypropylmethylcellulose E4M (×), F4M (◇) or K4M (■) measured using a thermal mechanical analyser in penetration mode (taken from Ref. [29]).

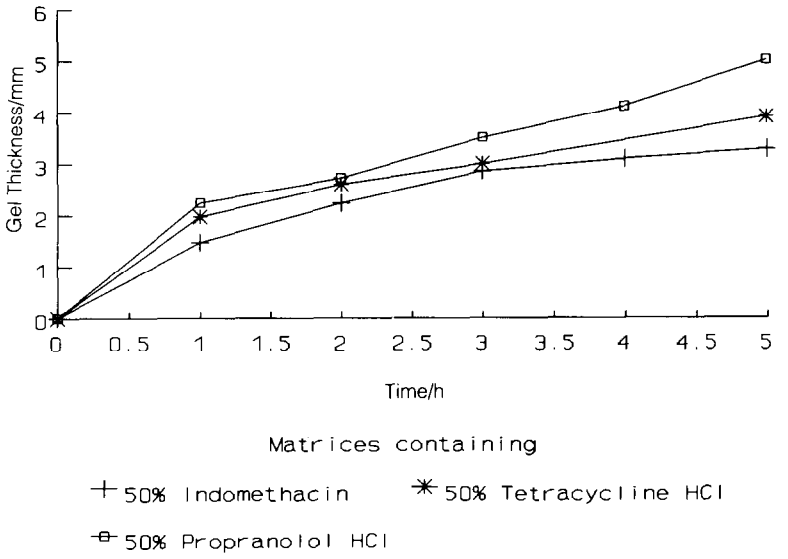

Fig. 7. The effect of time on the gel layer thickness of matrices containing 50% hydroxypropylmethylcellulose K4M and 50% of propranolol hydrochloride, tetracycline hydrochloride or indomethacin during contact with water at 37°C (taken from Ref. [31]).

cellulose ether, indicates that the thicknesses were similar despite apparent differences claimed for the polymers [22].

The incorporation of drug into the matrix altered the production of the gel layer (Fig. 7). The production of the gel layer in matrices containing propranolol or tetracycline hydrochloride was rapid over the first hour but was constant thereafter. Thicker gel layers were produced in the absence of drug. The thickness of the gel layers after 5 h ranked as propranolol > tetracycline > indomethacin which paralleled results measuring swelling of matrices.

Clearly, however, no account for the role of substitution type could be determined by thermal analysis for the role of substitution on release kinetics. However, it was equally apparent that the drug alters the hydration mechanisms of the cellulose ethers. Consequently gels containing HPMC K15 were evaluated by thermal analysis, in the absence and presence of a model drug, propranolol hydrochloride.

4. Thermal analysis of aqueous gels containing hydroxypropylmethylcellulose and propranolol hydrochloride

4.1. Materials and methods

The gels were prepared using hydroxypropylmethylcellulose (HPMC K15M), Methocel grade K15M (Dow Chemicals, USA), using glass distilled water, and the addition of propranolol hydrochloride B.P. as a model drug.

Gel preparation

Gels (20 g) were prepared by heating approximately one third of the total amount of distilled water to 80°C, adding the HPMC, and allowing it to disperse before adding distilled water or distilled water containing the required amount of propranolol hydrochloride. The gels were mixed in a mortar with a pestle, before cold distilled water was added to make up to the required weight. Gels were prepared to contain 10%, 20%, 30% or 40% w/w HPMC and 0%, 10%, 20% or 30% w/w propranolol hydrochloride; gels containing 40% w/w HPMC and 30% w/w propranolol hydrochloride were very difficult to prepare homogeneously and hence were not studied. Gels were either 2 h or 24 h old, storage taking place under ambient conditions in airtight containers.

Aqueous solutions of 10%, 20%, 30% or 40% w/w propranolol hydrochloride were also prepared. To ensure homogeneity, the samples were first heated to dissolve the propranolol hydrochloride and samples were transferred to sample pans before recrystallisation of the supersaturated solution occurred.

DTA

Gels (approximately 2 mg) were placed in sealed volatile sample pans (Perkin-Elmer), they were cooled to −25°C rapidly (uncontrolled) or at −5°C min^{-1}. They were then scanned at 10°C min^{-1} using a Stanton Redcroft 671 differential thermal analyser. Indium ($\Delta H_f = 28.4$ mJ g^{-1}) was used as calibrant and peak areas were measured by planimetry.

DSC

A Perkin-Elmer differential scanning calorimeter DSC7 (Beaconsfield, UK), with automatic cooling facilities was used, controlled by a Perkin-Elmer TAC7. The equipment was calibrated using indium and zinc. The samples were cooled from ambient, either rapidly (the DSC heads were cooled to −80°C and the sample was placed on the head; the sample cooled to the programmed temperature of −30°C from ambient in a matter of seconds) or slowly (samples were cooled at a controlled rate of −3°C, using liquid nitrogen).

Samples, weighing 10–20 mg, were taken at 2 h or 24 h after preparation. They were sealed in volatile sample pans (40 μl, Perkin-Elmer). Samples were subsequently heated at a rate of 10°C min^{-1} to 30°C in order to measure the melting enthalpy of free water. Melting enthalpies were automatically calculated by the instrument which reduced the errors associated with planimetry used with the data from DTA.

4.2. Results and discussion

Both the DSC and DTA methods were used in this study and all preliminary work was undertaken using DTA. Once the method was established, melting enthalpies were determined using DSC. The aim was to determine the amount of bound and free water in each gel. This was achieved by cooling the gels to below the freezing point of water in order to freeze the "free" water. Each sample was

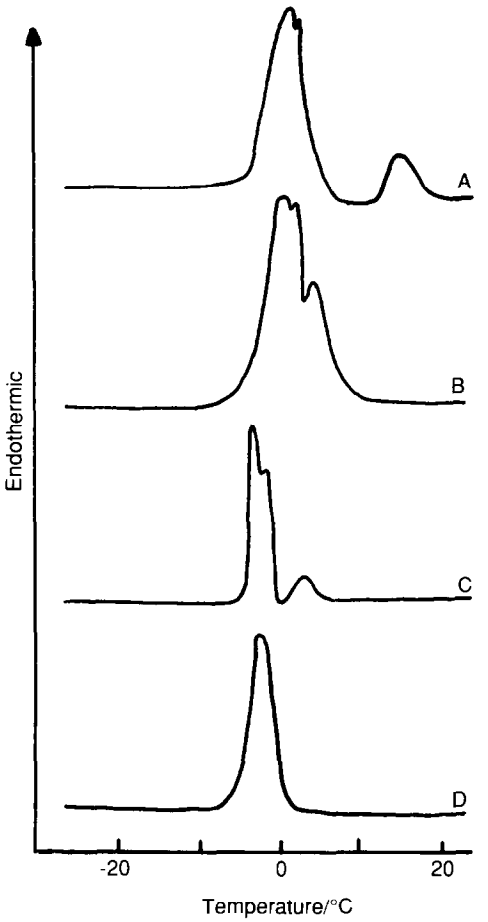

Fig. 8. DTA scans of various 2 h old gels containing hydroxypropylmethylcellulose K15M (HPMC K15M): curve A, 10% HPMC K15M, rapidly cooled; curve B, 10% HPMC K15M, rapidly cooled; curve C, 10% HPMC K15M, rapidly cooled; curve D, 10% HPMC K15M, cooled at 5 °C min^{-1}.

then heated and the enthalpy of melting of the "free" water at approximately 0 °C was measured. The method was then transferred to DSC; similar results were obtained using both sets of equipment. The DSC was considered more accurate because the cooling rates were more controllable than those of the DTA and the enthalpies were measured automatically, removing human error.

At first the gels were cooled rapidly (uncontrolled cooling), and the scans produced on subsequent heating showed inconsistent results. A typical scan obtained using the DTA method is shown in Fig. 8, curve A. Instead of a single endotherm centred around 0 °C which would be due to the melting of free ice, a double endotherm was apparent. Scans produced using this method of rapid cooling generally, but not always, produced a double endotherm centred around 0 °C which was poorly reproducible. Frequently a further endotherm was apparent.

Sometimes, this endotherm was sharp and distinct (Fig. 8, curve A) and on other occasions it was not (Fig. 8, curve B). This endotherm occurred between 0 and 20°C. The double endotherm at approximately 0°C and the appearance of the other endotherm between 0 and 20°C made it difficult to estimate the melting enthalpies of free water, especially since resolution between the second endotherm and the melting process at 0°C was not always complete.

It became apparent that the proportions given by these endotherms were "cooling related"; the faster the cooling rate, the larger the second endotherm. These two endotherms seemed therefore to be associated. Also the summated enthalpies for the peaks, cooled at different rates, were similar. It became clear that if the gels were cooled slowly (-5°C min^{-1}), the secondary endotherm and the double peak were not apparent and a single endotherm centred around 0°C was produced (Fig. 8, curves C and D).

The presence of a double endotherm at 0°C, along with a freezing-dependent endotherm shape, has been reported by Sung [9], who explained that there were three types of water in p(HEMA) hydrogels: bound, free and interfacial or lightly bound. The double peak was attributed to there being two kinds of water in the gel, free water and lightly bound water. The shape of the double peak was also dependent on freezing conditions, although how was not explained [9]. The presence of two types of free water may explain the double peaks shown in the scans of HPMC gels. For example, HPMC has polar sites which are capable of strongly hydrogen bonding to water which may also be capable of weakly bonding to less polar sites. The double character of a melting peak centred at 0°C has also been reported by Roorda et al. [7]. They indicated that the double peak was not due to different types of water but to the development of a metastable non-equilibrium situation formed on cooling the gels. Nakamura et al. [6] also reported a double peak around 0°C when studying water in cellulose samples. Like Sung [9], they attributed the presence of this double peak to three kinds of water in the gels. The precise nature of this double peak in HPMC gels remains a point of conjecture.

One possible explanation for the presence of the second endotherm at 0–20°C may be that the polymer supercooled on rapid cooling; this could force the polymer to coil and form an unnatural tertiary structure held together, possibly by hydrogen and van der Waal bonds. By forming this high energy structure, water could be trapped within the structure itself. On scanning an endotherm consistent with melting ice (approximately 0°C) was obtained. As the temperature rises further, bonds holding the structure together would break thus allowing mobility into the chain and releasing energy, and more importantly, the trapped water. If the gel is allowed to cool slowly an organised structure is formed with minimum energy, and on heating a single endotherm is present. Alternatively, the secondary peak may represent a mesomorphic transition. Hatakeyama et al. [34] reported conversion of the liquid crystal state to the isotropic state in gels containing the ionic cellulose polymer, sodium carboxymethylcellulose. Nonetheless, slow cooling was utilised to remove this secondary transition and allow estimation of the amount of water associated with HPMC.

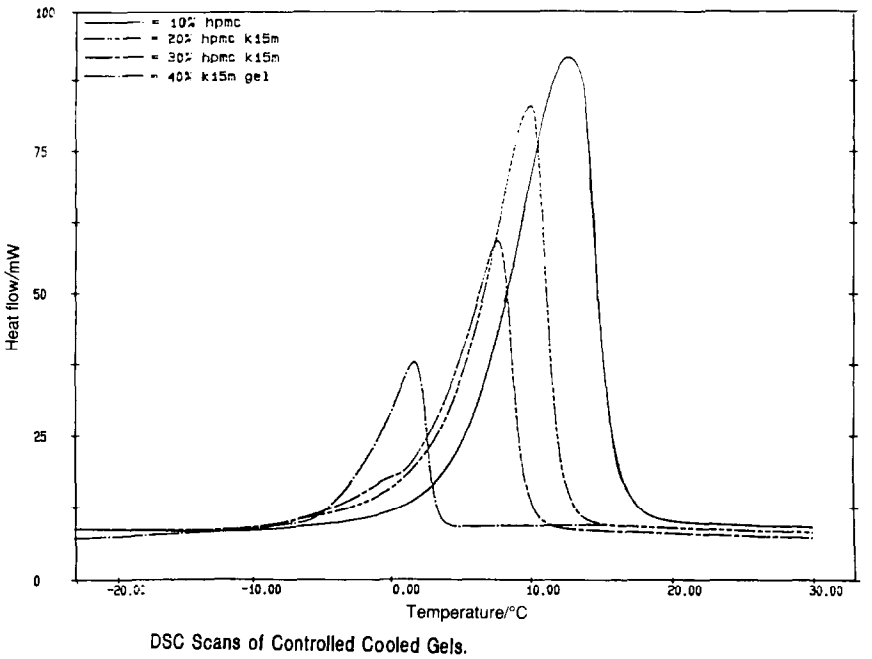

Fig. 9. DSC scans of 2 h old gels containing 10, 20, 30 or 40% hydroxypropylmethylcellulose K15M (HPMC K15M), cooled at 3°C min^{-1}.

Using DSC, all scans were carried out using slow cooling rates (-3°C min^{-1}; the Stanton Redcroft DTA would not function at such a low cooling rate) to avoid the occurrence of secondary endotherms and double peaks and to obtain reproducible data. Fig. 9 shows typical DSC scans of gels containing 10, 20, 30 and 40% HPMC K15M and Table 1 shows the results for the melting enthalpies of gels containing 0–40% HPMC K15M and 2 h old. The values of the melting enthalpy decreased as the concentration of HPMC in the gel increased. It is commonly accepted that there are at least two thermodynamically different types of water in gels, bound and free. According to Sung [9] the amount of bound water within a gel is constant. Once all binding sites are occupied any excess water then is either lightly bound or free. Fig. 10 shows that there was a straight line relation between the free water detected and polymer concentration in the absence of propranolol hydrochloride; it was therefore possible to extrapolate the plot to zero enthalpy. The concentration at this point represents the minimum ratio of HPMC:water that is required for water to occupy the binding sites of HPMC K15M, i.e. giving complete hydration of HPMC. Any water added after this would become measurable by DSC. Extrapolation of the plot to zero enthalpy by linear regression ($r = 0.993$) indicates the composition of fully hydrated HPMC (all water present is bound) is 55.7% HPMC K15M:44.3% water. Any further water added to the gel after this would be classed as free water. Preliminary studies using the Stanton Redcroft thermal analyser gave a value of 51.2% HPMC K15M:48.8% water [23].

Table 1
Melting enthalpies of free ice in gels after 2 and 24 h storage ($n = 2$)

Composition of gel [a]	Melting enthalpy/J g^{-1}	
	2 h	24 h
Distilled water	325.1	325.1
10% HPMC	242.8	265.7
20% HPMC	204.9	230.2
30% HPMC	137.6	162.0
40% HPMC	95.6	114.6
10% PH	270.7	270.1
10% PH 10% HPMC	210.5	222.0
10% PH 20% HPMC	167.1	181.1
10% PH 30% HPMC	121.7	132.6
10% PH 40% HPMC	102.1	102.1
20% PH	223.4	223.9
20% PH 10% HPMC	184.3	191.6
20% PH 20% HPMC	130.0	140.3
20% PH 30% HPMC	80.6	85.8
20% PH 40% HPMC	47.1	47.0
30% PH	165.8	166.0
30% PH 10% HPMC	154.6	159.1
30% PH 20% HPMC	107.4	111.2
30% PH 30% HPMC	51.6	51.9

[a] PH is propranolol hydrochloride.

Typical DSC scans of HPMC K15M gels containing 10% propranolol hydrochloride are shown in Fig. 11. This shows one scan where the gel was cooled rapidly (Fig. 11, curve A) and one in which the gel was cooled at 3°C min^{-1} (Fig. 11, curve B). Gels containing propranolol hydrochloride were just as likely to produce the secondary endotherm as gels which contained only HPMC and water, when cooled rapidly. With cooling rates of 3°C min^{-1} again only one endotherm, centred around 0°C, was apparent. All gels were therefore cooled at a rate of 3°C min^{-1}.

In the presence of propranolol hydrochloride, the plots of enthalpy versus HPMC content were complicated (Fig. 10). Whilst the data for gels containing 20% propranolol hydrochloride showed an apparent straight line relationship with HPMC content, the data for gels containing 10% propranolol showed a positive deviation from linearity (see also Ref. [23]) and the data for gels containing 30% showed an initial lag in the decrease of measured enthalpy.

It will be equally apparent from Table 1 that the addition of propranolol hydrochloride in the absence of HPMC decreased the enthalpy associated with water melting at 0°C. The relationship between enthalpy and composition was a linear one. Extrapolation to zero enthalpy indicated a composition of 61.9:38.1 propranolol hydrochloride:water (equivalent to 1:10 molar ratio).

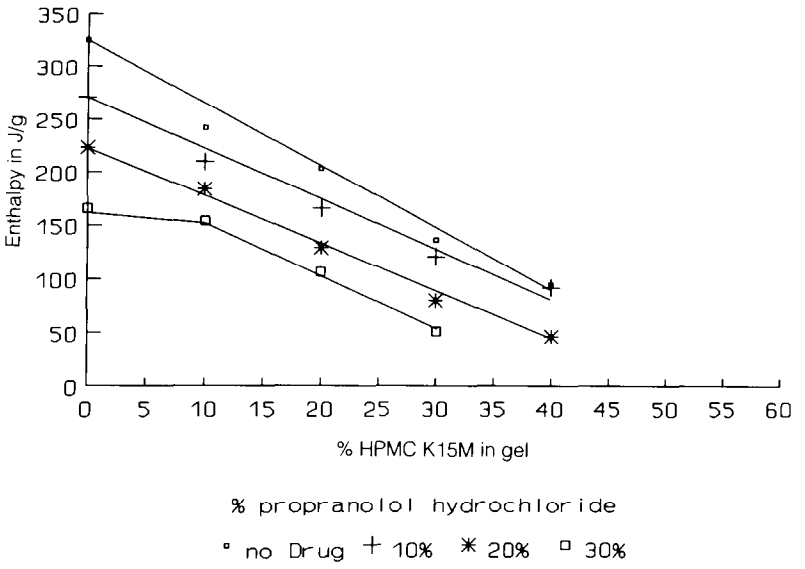

Fig. 10. The effect of composition of 2 h old gels containing hydroxypropylmethylcellulose K15M (HPMC K15M) and propranolol hydrochloride, on the enthalpy of melting water: ◦, no propranolol hydrochloride; +, 10% propranolol hydrochloride; *, 20% propranolol hydrochloride; □, 30% propranolol hydrochloride.

Careful perusal of Fig. 10 and Table 1 indicates that in the mixtures containing both propranolol hydrochloride and HPMC, the melting enthalpies of free water are higher than anticipated solely on knowledge of composition and the water associated with propranolol hydrochloride or HPMC in solutions containing only drug or polymer. Therefore less water was required to fully hydrate the HPMC when propranolol hydrochloride was added to the gel. Propranolol hydrochloride salts in HPMC K15M [20,31] thus making the polymer more soluble, it may be that in making the polymer more soluble, less water is required to bind strongly to the polymer and a greater proportion of the water in the gel is free water. Such a hypothesis concurs with the increase in cloud point of HPMC gels instigated in the presence of propranolol hydrochloride.

Interestingly, Joshi and Wilson [35] have examined the dissolution of HPMC E5 and ethyl cellulose E4 into water via calorimetry. DSC was used to examine partially hydrated gels and mechanisms of dissolution proposed to account for the dissolution process based on DSC data and microcalorimetry. Moles of non-freezing water per polymer repeat unit (PRU) were 6.2 ± 1.3 for HPMC E5. Using a value of Dow Chemicals for the PRU of 192 for HPMC K grades, and the intercept value for zero enthalpy of gels containing HPMC K15M and water of 55.7:44.3 HPMC:water and the molecular weight of water as 18.02, it can be estimated from this study that the moles of non-freezing water per PRU were 8.5, a value in the same range as that previously reported [35].

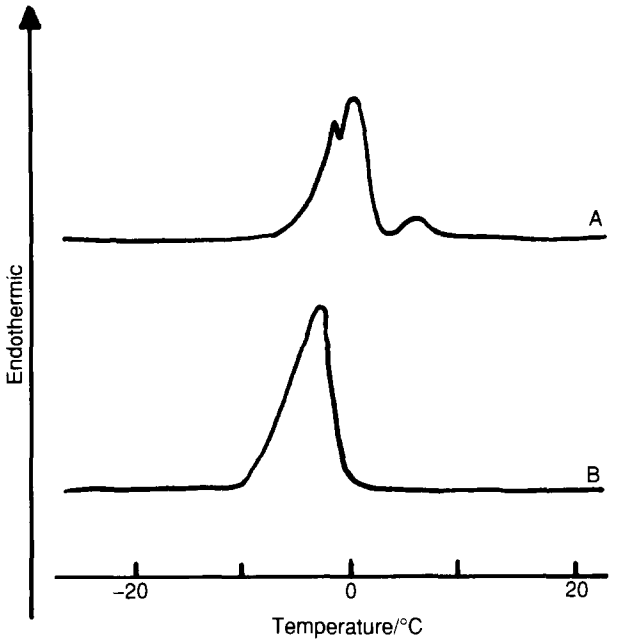

Fig. 11. DSC scans of gels containing 10% hydroxypropylmethylcellulose K15M (HPMC K15M) and 10% propranolol hydrochloride: curve A, rapid cooling; curve B, cooling at 3°C min^{-1}.

The total amount of free water increased in the samples that were tested 24 h after preparation from those that were tested 2 h after preparation (Table 1) indicating that a small amount of water is released during storage. The mechanism may have been gel syneresis. The level of increase in free water in the gels after 24 h of storage generally decreased with an increase in either HPMC K15M or propranolol hydrochloride content. This could possibly be due to there being less elastic recovery within these gels. Gel syneresis is common in dilute gels [36]. Dusek and Sedlacek [37] showed that syneresis in p(HEMA) gels could take place at high polymer concentrations (50% polymer to water). The increases in enthalpy which occurred over 24 h show that the gel is a dynamic system which did not equilibrate for some time, as shown by Neely [38] who reported that both HPMC and methylcellulose were capable of forming aggregates in gels over a period of 48 h. Extrapolation to zero enthalpy indicated that the composition by linear regression ($r = 0.997$) of the fully hydrated HPMC K15M gels was 61.8:38.2% HPMC K15M:water for the 24 h old gel, confirming that more free water was present in the older sample. This equated to 6.6 moles of bound water per PRU of polymer.

5. Conclusions

Using cellulose ethers as model polymers, thermal analysis clearly shows that interactions between drug and polymer occur in the hydrating gel layer around a

matrix tablet and are, at least, partly responsible for the modulation of drug release. DSC can be used to assess the rate and extent of water uptake and TMA can be used to determine the rate and extent of tablet swelling and gel layer formation. The interaction between water and HPMC in the absence and presence of drugs can also be shown to exist, although the precise quantification of these amounts requires techniques other than thermal analysis. The application of the techniques reported in this review to other polymer–water systems is, at present, unreported.

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