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The influence of HPMC substitution pattern on solid-state properties

Mikael Larsson[a,*], Anna Viridén[a], Mats Stading[b,c], Anette Larsson[a]

[a] Department of Chemical and Biological Engineering, Chalmers University of Technology, 41296 Göteborg, Sweden
[b] Department of Materials and Manufacturing technology, Chalmers University of Technology, 41296 Göteborg, Sweden
[c] Structure and Material Design, SIK – The Swedish Institute for Food and Biotechnology, PO Box 5401, 40229 Göteborg, Sweden

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ABSTRACT

The solid-state properties were studied for different batches of hydroxypropyl methylcellulose (HPMC). The batches had similar chemical composition, but different degree of heterogeneity with regard to the distribution of the substituents along the polymer chains. The glass transition temperature, T_g, was analysed using a new developed method where dynamic mechanic analysis, DMA, was performed in compression mode on compacts, utilizing a wedge-shaped probe. The method was verified by conventional DMA on films. Molecular interactions were studied using FT-IR. In addition, the water vapour sorption was determined by gravimetric measurements and the plasticization by water vapour was studied on film samples using DMA. The results revealed a linear relationship between increasing T_g and increasing percent glucose liberated after enzyme hydrolysis. The percent glucose liberated can in turn be considered to account for both the heterogeneity of the substituents and the total degree of substitution. The results indicated that more heterogeneously substituted cellulose derivatives and derivates with a lower degree of substitution had stronger interactions between polymer chains. As expected from these results, some small difference in the plasticization by water vapour could be detected. However, no significant differences were found in molecular interactions using FT-IR or in the sorption of water vapour. The correlation between heterogeneity in the distribution of the substituents and T_g is of much interest as heterogeneously substituted batches of HPMC have been previously shown to exhibit very different behaviour in solution and in gelling tablets.

1. Introduction

Cellulose ethers are a commercially important class of polymers, which are produced on a large scale and used in a variety of fields. They are for example used in food, cosmetic, construction and oil industries as thickeners, binders and emulsifiers (Brandt, 2002; Clasen & Kulicke, 2001). Within the pharmaceutical field, cellulose ethers are commonly used as rate controlling agents for drug release and are thus found in various formulations such as film coatings and tablet preparations (Kibbe, 2000). Since the rate of hydration as well as the solution properties of the polymers determines the rate of drug release, they are both very important parameters for the functionality of the polymers. Furthermore, the performance of polymers in such applications must be predictable and reproducible. Therefore, the functional related characteristics of the polymers used must be well defined.

Hydroxypropyl methylcellulose (HPMC) is an example of a polymer used in extended release formulations (Kibbe, 2000). Critical parameters for the polymers in such formulations have been attributed to the solubility and the viscosity of the polymer solution (Alderman, 1984; Gao et al., 1996; Ju, Nixon, & Patel, 1995; Kavanagh & Corrigan Owen, 2004; Koerner, Larsson, Piculell, & Wittgren, 2005; Narasimhan, 2001), which is rendered by the degree of substitution and the molar mass. Commercially available pharmaceutical grades of HPMC can be regarded as quite polydisperse materials. This can partly be ascribed to the polymer originating from cellulose, thus having a natural variety in molar mass. However, from the specifications of the pharmaceutical grades are neither the molar mass nor its distribution offered, instead the viscosity is provided (European Pharmacopoeia, 2005; United States Pharmacopeia, 2008). Another parameter which affects the properties of the polymer is the degree of substitution. HPMC is substituted with both methoxy and hydroxypropoxy groups. The methoxy group is more hydrophobic than the hydroxypropoxy group and by varying the amount of the two substituents different solubility of the polymer is obtained. In order to obtain a polymer with the desirable properties there are different viscosity and substituent grades available (European Pharmacopoeia, 2005; United States Pharmacopeia, 2008). However, a selection of a proper grade has not always proven to give predictable release

* Corresponding author. Tel.: +46 31 772 34 11; fax: +46 31 772 34 18.
E-mail address: mikael.larsson@chalmers.se (M. Larsson).

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rates from hydrophilic matrix tablets and batch-to-batch variations are frequently seen (Dahl, Calderwood, Bormeth, Trimble, & Piepmeier, 1990; Viriden, Wittgren, Andersson, & Larsson, 2009). The batch-to-batch variation can to some extent be explained by the broad specifications of the viscosity and degree of substitution (Dahl et al., 1990), but also to the distribution of the substituents (Viriden, Wittgren, Andersson, & Larsson, 2009). The distribution of substituents can alter in many ways (Mischnick, 2001; Richardson & Gorton, 2003). For example the distribution can vary within the glucose unit, regarding which of the three hydroxyl groups on the glucose unit that has been substituted. Furthermore, because the hydroxypropoxy group can propagate, both the length and chemistry can alter depending on the production route. Additionally, within a batch the substituent pattern can further vary along the polymer chains and between individual chains, giving a rather complex structure. Not surprisingly, the substituent pattern has shown to affect the solution properties of cellulose derivatives (Burchard, 2003; Fitzpatrick et al., 2006; Haque, Richardson, Morris, Gidley, & Casell, 1993; Neely, 1963; Schagerloef et al., 2006; Schulz, Burchard, & Donges, 1998; Viriden, Wittgren, Andersson, Abrahmsen-Alami, & Larsson, 2009), where for example aggregate formation have been ascribed to the heterogeneous substituent pattern. A way to characterize the substitution pattern of cellulose derivates is selective enzymatic hydrolysis, followed by the analysis of the hydrolysis product. Briefly, a high percentage of liberated non-substituted glucose units corresponds to a more heterogeneous distribution of the substituents (Karlsson et al., 2002; Schagerloef et al., 2006). Viriden et al. have shown, based on such enzyme hydrolysis analysis, that HPMC batches with heterogeneous substituent pattern along the chain behaved more associative and thus formed larger polymer structures in solution which increased the viscosity and hence decreased the polymer release from hydrophilic matrix tablets (Viriden, Wittgren, Andersson, & Larsson, 2009).

Another parameter that is of great importance in numerous applications for polymers is the glass transition temperature (T_g), the temperature at which the thermal motion of the main polymer chains overcomes the chain to chain interactions and allows for larger chain movement, with changed mechanical and mass transport properties as a consequence (Gedde, 1995; Grinsted, Clark, & Koenig, 1992). It is well known that the T_g of polymers is dependent on molecular weight, interactions, flexibility and the bulkiness of side-groups (Gedde, 1995). Despite the importance of T_g and the widespread use of HPMC, there are only a few studies available on the connection between HPMC molecular characteristics and the T_g. For relatively low molecular weight HPMC the T_g has been shown to be affected by the molecular weight (Kararli, Hurlbut, & Needham, 1990). Furthermore, Gomez-Carracedo, Alvarez-Lorenzo, Gomez-Amoza, & Concheiro (2003) has studied the influence of methoxy and hydroxypropoxy substitution on the T_g of cellulose ethers. They came to the conclusion that hydrogen bonding is a main factor influencing the T_g of cellulose ethers, and that a high methoxy/hydroxypropoxy ratio corresponds to a lower T_g. However, differences in this ratio could not explain all of their data. To the authors knowledge there is to date no theory available that is really successfully in correlating the T_g of HPMC to the molecular characteristics. Taking into account the fact that HPMC can have a heterogeneous substitution pattern (Viriden, Wittgren, Andersson, Abrahmsen-Alami, et al., 2009; Viriden, Wittgren, Andersson, & Larsson, 2009) and that it has been shown that hydrogen bonds can increase the T_g of copolymers (Kuo & Tsai, 2009; Kuo, Xu, Huang, & Chang, 2002), it was considered possible that the heterogeneity of the substituents, from which the different solution and gelling behaviour originates, would also influence the T_g.

The aim of this study was to compare the solid-state properties of two batches of HPMC of the same pharmaceutical grade, but with distinct differences in polymer release profile from tablets, gelling properties and behaviour in solution. The differences have previously been attributed to differences in the substitution pattern (Viriden, Wittgren, Andersson, Abrahmsen-Alami, et al., 2009; Viriden, Wittgren, Andersson, & Larsson, 2009). The solid-state characteristics investigated were; glass transition temperature, water vapour sorption, plasticization by water vapour and molecular interactions. In addition, to further develop on the results observed in the glass transition analysis, another two batches of the same pharmaceutical grade were analysed with regard to their glass transition and were included in the discussion on the correlation between the T_g and chemical characteristics of HPMC. All of the batches used in this study have previously been thoroughly characterized by Viriden, Wittgren, Andersson, Abrahmsen-Alami, et al. (2009), Viriden, Wittgren, Andersson, and Larsson (2009), Viriden, Wittgren, and Larsson (2009), with regard to their molecular characteristics. The methods used in this study were DMA for the analysis of T_g and plasticization by water vapour, gravimetric analysis for the determination of water vapour sorption and for thermal decomposition analysis, and Fourier transform infrared spectroscopy for the analysis of molecular interactions.

2. Materials and methods

2.1. Materials

Four batches of HPMC, A–D, of the same pharmaceutical grade (USP 2208, 100 cps, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan and Dow Chemical Co., USA), with the molecular characteristics in Table 1, were used. KBr used was of analytical grade (Sigma–Aldrich, St. Louis, MO, USA). Water used was of Milli-Q grade.

2.2. Film preparation

HPMC films for the two batches A and B were simultaneously prepared as follows.

For DMA and thermogravimetrical analysis 2% HPMC solutions were prepared by mixing HPMC powder with Milli-Q water and allowing the solutions to stir for 1 week at room temperature and 1 week at 6 °C. From the solutions 15 g were poured into 100 ml Weigh boats (VWR, Stockholm, Sweden), for the batch A and B, respectively. The films were then acquired by drying the solutions at 30 °C in the same desiccator with freshly dried Silica gel orange

Table 1
Polymer characteristics of the HPMC batches. Data from the article by Viriden, Wittgren, Andersson, and Larsson (2009).

Sample	Mw[a] ($\times 10^4$ g/mol)	Mw/Mn[a] (g/mol)	%[b] HPO	%[b] MeO	% glucose units (enzymatic hydrolysis)[a]
A	12.4 (0.1)	2.8 (0.5)	10.9	23.3	0.9 (0.1)
B	10.4 (0.2)	2.2 (0.3)	7.0	24.6	1.4 (0.1)
C	9.1 (0.01)	1.9 (0.2)	6.6	24.1	1.2 (0.1)
D	14.1 (0.3)	2.8 (0.6)	10.9	23.4	0.3 (0.1)

[a] The results given are mean values and corresponding standard deviations within parentheses ($n = 3$).
[b] RSD of 0.02 according to an in-house validation.

(Sigma–Aldrich, Steinheim, Germany) for 10 days, the silica gel was replenished every 3 days. The films were stored in a desiccator with Silica gel orange in between measurements.

The films for FT-IR were prepared by diluting the 2% HPMC solutions for the batches A and B to 0.4%. From the diluted solutions 2 g were poured into 7 ml weigh boats (VWR, Stockholm, Sweden). The films were then formed by drying the samples for 4 days in a desiccator with freshly dried Silica gel orange.

2.3. FT-IR

Film and powder samples to be used in the FT-IR analysis were prepared for analysis by drying in a vacuum oven (Forma Scientific Inc., Marietta, OH, USA) at a negative pressure of about 100 kPa and 40 °C for 3 h. The powder samples were mixed with KBr using a mortar and subsequently pressed to compacts at 10^4 kg under vacuum before analysis. The film samples were cut to suitable size before being mounted for analysis. All samples were analysed between 4000 and 400 cm^{-1} using a System 2000 FT-IR spectrophotometer (Perkin Elmer, Beaconfield Bucks, England).

2.4. Thermogravimetric analysis

Thermogravimetric analysis was performed on film and powder samples using a TGA 7 Thermogravimetric analyzer (Perkin Elmer, Norwalk, CT, USA). The sample weights analysed were in the interval 2.4–4.3 mg. The analyses were performed in air and in N_2 by initially keeping the samples at 140 C for 10 min, subsequently performing a temperature scan between 140 and 400 °C at a rate of 2°/min.

2.5. Dynamic mechanic analysis

DMA measurements were performed using a Rheometrics RSAII (Rheometrics Scientific, Piscataway, NJ, USA) with an external air moisture controlling device (Stading, 1998). The temperature was calibrated using the well known melting points of Gallium and Indium. The deformation and the force response of the samples were monitored and from those parameters the elastic modulus, E', and the loss factor, tan(δ) were calculated.

For the DMA analysis of films, samples were prepared to a width of 3 mm for plasticization analysis and 6 mm for thermomechanical analysis using a razor-edged punch. The sample thickness was recorded as the average of three measurements. The effective initial sample length in the DMA was 21–23 mm. The samples were analysed in strain controlled stretching at a frequency of 1 Hz in the linear strain region.

For the DMA analysis of powder, samples were prepared by compressing about 40 mg powder to 2.5 mm radius compacts under an applied force of 400 N using a TA-HDi® (Stable Microsystems, Godalming, United Kingdom). The samples were analysed in DMA strain controlled compression mode at a frequency of 1 Hz, utilizing a wedge-shaped probe with the setup shown in Fig. 1.

Thermomechanical analysis of samples was performed in two steps. First initial temperature scans were performed between 30 and 180 °C at 10°/min; the first scan was to remove the water in the sample, the second scan was used for the interpretation of the data. From the initial temperature scan the region of interest, with regard to plasticizing, was observed to be at temperatures greater than 140 °C. Samples were further analysed by initially keeping the samples at 140 °C for 10 min to remove the water in the samples and then performing temperature scans between a temperature of 140–240 °C at 2°/min.

The plasticizing effect of water at ambient temperature (about 26 °C) was analysed in two steps. First initial relative humidity (RH) scans were performed at RH in the range 20–95%. From those RH scans, the region of interest was observed to be at RH above 90%. Further plasticizing studies were performed in the following steps: 10 min at 20% RH, 15 min at 90% RH, 25 min (or until the sample elongation reached the limit of the instrument) at 95% RH and finally 17 min at 20% RH. The samples elongated on an RH increase and were kept at each RH until being considered having reached equilibrium length, except at 95% RH at which the samples were continuously stretched due to their rubbery state.

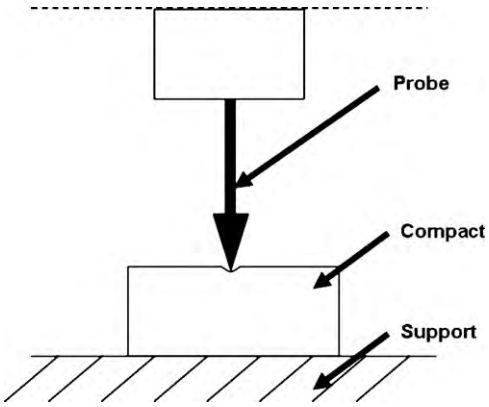

Fig. 1. Schematic drawing of the setup for DMA analysis of compacts using a wedge-shaped probe.

2.6. Water vapour sorption measurements

The equilibrium water sorption was analysed as a function of RH using a Q5000 v3.3 (TA Instruments, New Castle, DE, USA). The analyses were performed on 4.6 mg of powder from each batch, at a temperature of 25 °C. The samples were initially held at 0% RH and were subsequently equilibrated in RH steps of 10–90%, finally the samples were equilibrated at 95% RH, before once again being equilibrated at every 10% RH down to a final RH of 20%. As equilibrium condition a sample weight change of less than 0.002 mg over 5 min, was applied. At each RH the sample weight was recoded, and the water content calculated.

3. Results and discussion

3.1. FT-IR analysis

The two HPMC batches A and B have previously been reported to exhibit remarkably different properties in solution and in applications such as swelling of and release from hydrophilic matrix tablets (Viriden et al., 2009a; Viriden et al., 2009b; Viriden, Wittgren, Andersson, Abrahmsen-Alami, et al., 2009; Viriden, Wittgren, Andersson, & Larsson, 2009; Viriden, Wittgren, & Larsson, 2009). Those differences were proposed to derive from differences in polymer–polymer interactions, which in turn originate from the heterogeneous distribution of the substituents. In order to investigate if any difference in polymer–polymer interactions could be detected between the batches, they were analysed using FT-IR. The acquired spectra showed appearances very similar to those reported for HPMC by others (Anuar, Wui, Ghodgaonkar, & Taib, 2007; Gustafsson, Nystrom, Lennholm, Bonferoni, & Caramella, 2003; Wang & Xu, 2006). When comparing with literature spectra for methylcellulose and hydroxypropylcellulose (Hummel, 1984) it could be seen that the HPMC spectra were similar to the spectrum for methylcellulose. This is not surprising as the degree of methoxy substitution is much higher than the degree of hydroxypropoxy substitution. The IR spectra of powder from the two batches did not display any significant differences, as can be seen in Fig. 2. For the analysed film samples, the transmittance was zero for the most

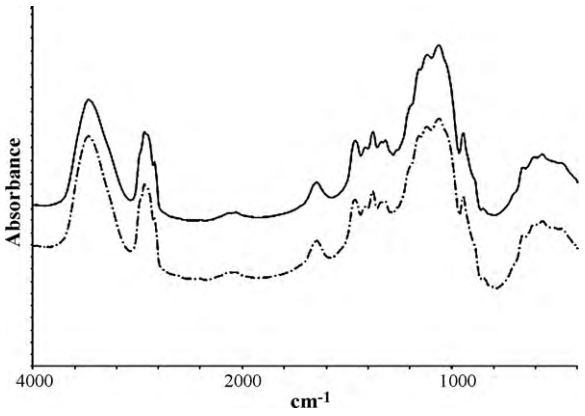

Fig. 2. FT-IR spectra of the batches A (dashed) and B (solid).

strongly absorbing region with the peak around 1100 cm^{-1}, this broad peak includes signals from C–O–C stretches, secondary alcohols and methoxy groups (Gustafsson et al., 2003). However, the spectra from the films did show identical appearance with high resolution in the other regions of the spectra (results not shown). Based on the results from both powder and film samples, it is concluded that any batch specific interactions, due to the chemical heterogeneity, are either to few or not frequent enough to give a distinct signal in a FT-IR spectrum.

3.2. Thermogravimetric analysis

In order to establish the maximum temperature and conditions at which samples could be reliably analysed without risk of decomposition in the thermomechanical analysis, samples from the batches A and B were subjected to thermogravimetric analysis in air and in N_2, both in the form of powder and in the form of the prepared films. The initial holding time and rate of temperature increase being the same as that used for the thermomechanical analyses.

From the results (not shown) in the thermogravimetrical analysis it was concluded that the samples could be analysed up to temperatures of at least 230 °C in air and 250 °C in N_2 without risk of thermal decomposition influencing the results. Since the glass transitions of the samples were expected to occur at temperatures lower than 230 °C, the thermomechanical analysis was conducted in air.

3.3. Thermomechanical analysis

The T_g of a polymeric material is correlated to the interactions present in the material. It has been shown that hydrogen bonds can increase the T_g of copolymers (Kuo & Tsai, 2009; Kuo et al., 2002) and that hydrogen bonding is a main factor influencing the T_g of cellulose ethers such as HPMC (Gomez-Carracedo et al., 2003). To investigate if any difference could be detected in the T_g between batches, and if a potential difference could be correlated to differences in molecular characteristics, the batches were subjected to thermomechanical analysis using DMA. First, the temperature at which the HPMC samples starts to become rubbery was determined from two subsequent temperature scans between 30 and 180 °C at a rate of 10°/min for film samples from batch A and B (results not shown).

For the batches A and B both film samples and compacts were analysed with regard to their T_g and the onset of the glass transition. The T_g for each run was taken as the temperature at the maximum of tan(δ) and the onset was determined from the intersect of the linear fits to the values of E' before and during the glass transitions. There was a significant difference in both T_g and onset temperatures between batch A and B as shown in Table 2, and Fig. 3. Batch A exhibits a T_g and onset temperature roughly 10 °C lower than batch B. Furthermore, it can be concluded that the analyses of films and compacts gives approximately the same results. The small differences are most likely due to the different thermal history between samples and not due to experimental factors; especially since the differences between the analysis methods is opposite for the two batches. Batch A displays an average T_g 0.3 °C higher when analysed as films, than when analysed as compacts. Batch B, instead displays an average T_g 2.9 °C lower when analysed as films, as compared to when analysed as compacts. Since the analysis of compacts proved highly accurate and reproducible, there are many advantages with this method compared to analysing films. Such advantages are reduction of sample preparation and analysis of the samples as received from manufacturers, thus eliminating artefacts from the preparation of films. DMA analysis of powder using a special sample holder (Mahlin, Wood, Hawkins, Mahey, & Royall, 2009) and oscillatory rheometry on compacts (Gomez-Carracedo et al., 2003; Gomez-Carracedo, Alvarez-Lorenzo, Gomez-Amoza, & Concheiro, 2004) have also been previously reported to be successful and accurate. Therefore, further thermomechanical analyses were performed on compacts.

HPMC varies greatly in the degrees of substitution, molecular weight and substitution pattern. In order to better be able to correlate the T_g to the molecular characteristics, two more batches (C and D) were analysed with regard to their T_g and onset temperature.

From the T_g values in Table 2, the following order of the T_g is acquired for the batches; $T_g^D = 182.8 < T_g^A = 192.5 < T_g^C = 201.9 < T_g^B = 203.0$ °C. Those T_g's are to be compared with previously reported T_g values for HPMC, being in the range 160–200 °C, depending on the molecular characteristics of the analysed sample and method used (Gomez-Carracedo et al., 2003; Kararli et al., 1990; Mahlin et al., 2009; McPhillips, Craig, Royall, & Hill, 1999; Nyamweya & Hoag, 2000; Zhang et al., 2009).

To elucidate the dependence of T_g on the molecular characteristics, molecular weight, degree of substitution and substitution pattern each of those are first considered separately.

The T_g's dependence on molecular weight has been described by the equation (Edwards, 1994; Fox & Flory, 1950):

$$T_g = T_{g_\infty} - \frac{k}{M} \quad (1)$$

where $T_{g\infty}$ is the T_g of a molecule of infinite molecular weight, k is a constant and M is the molecular weight. Eq. (1) shows that differences in T_g derived from differences in molecular weight should be small for large molecular weights. Kararli et al. (1990) have reported a 5 °C difference in the glass transition of HPMC sam-

Table 2
Glass transition temperature (T_g) and onset temperature for the glass transition (T_o).

Batch	A		B		C	D
Sample type	*Films*	*Compacts*	*Films*	*Compacts*	*Compacts*	*Compacts*
T_g[a]	192.8 (0.86)	192.5 (0.59)	200.1 (0.95)	203.0 (0.26)	201.9 (0.76)	182.8 (0.40)
T_o[a,b]	173 (1.2)	169 (1.2)	180 (1.2)	183 (2.1)	184.4 (0.71)	165.9 (0.34)

[a] The results given are mean values and corresponding standard deviations within parentheses (films: $n = 4$ and compacts: $n = 3$).
[b] Onset temperatures are acquired from the intersection of the extrapolations of the regions prior to and during the transition.

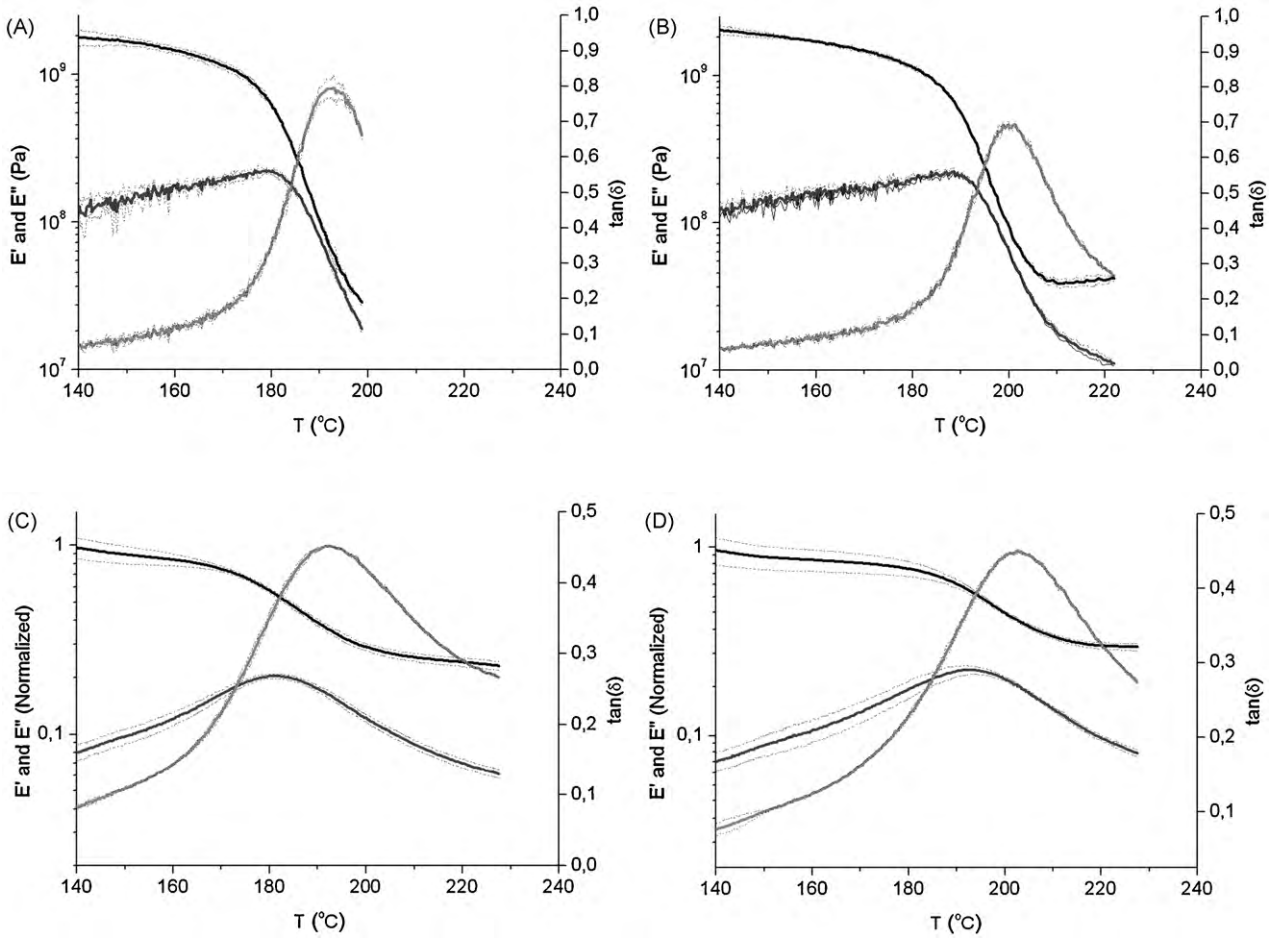

Fig. 3. The graphs display the thermomechanical properties for; (a) film samples from batch A, (b) film samples from batch B, (c) compacts from batch A and (d) compacts from batch B. The curves are elastic modulus (black), viscous modulus (dark grey) and tan δ (light grey). The moduli of the compacts have been normalized against the maximum value of E'. One standard deviation is indicated by dashed lines ($n = 4$ for films and $n = 3$ for compacts).

ples with molecular weights of 1×10^4 and 1.5×10^4 g/mol. For the batches in this study the largest difference in molecular weights is between the batches C and D, with molecular weights of 9.1×10^4 and 14.1×10^4 g/mol, respectively. This suggests that any contribution from molecular weight to differences in T_g should be very small for the batches in this study. However, if the molecular weight is considered, the following order of the T_g values is expected for the batches: $T_g^C < T_g^B < T_g^A < T_g^D$, which in no way correlates to the observed T_g values. In fact, the order of the observed T_g values for the batches C and D, having the biggest difference in molecular weight, is opposite of that suggested by their molecular weights.

The influence of the methoxy and hydroxypropoxy substituents on the glass transition of methyl cellulose, hydroxypropyl cellulose and HPMC has been studied by Gomez-Carracedo et al. (2003). They mentioned that in general, increasing degree of substitution lowers the T_g of cellulose ethers. Furthermore, they came to the conclusion that for HPMC the ratio of methoxy/hydroxypropoxy groups is influencing the T_g in such a manner that samples with a higher ratio have lower T_g. The explanation given is that both of the substituents disrupt the cellulose hydrogen bonding structure. However, the hydroxypropoxy substituents can partake in hydrogen bonding, whilst methoxy substituents cannot. Further examining their data, it is seen that the correlation between the methoxy/hydroxypropoxy ratio and T_g is not valid for the samples from the batches E4M and F4M. Also, looking at the methoxy/hydroxypropoxy ratio for the batches under comparison in this study (Table 1), it is seen that the batches (B and C) with the highest methoxy/hydroxypropoxy ratio actually have the highest T_g values. We do not disagree with the conclusion of Gomez-Carracedo et al. (2003) that a high methoxy/hydroxypropoxy ratio corresponds to a lower T_g. However, we do want to stress that this should only be valid for samples with a similar total degree of substitution. For samples that differ in the total degree of substitution both total substitution and the ratio between the substituents needs to be considered. For the samples in this study, the total degree of substitution suggests the following order of the T_g values; $T_g^D \approx T_g^A < T_g^B < T_g^C$ and the methoxy/hydroxypropoxy ratios suggests the following order of the T_g values: $T_g^C < T_g^B < T_g^D \approx T_g^A$. It is recognised that the total degree of substitution to some extent can explain the T_g values of the batches in this study, in particular the degree of substitution can explain the differences between the batches having a lower degree of substitution (B and C) and higher T_g values, and the batches having a higher degree of substitution (A and D) and lower T_g values. However, neither the total degree of substitution nor the methoxy/hydroxypropoxy ratios can satisfactory explain all observed differences in the T_g values.

The fact that the difference in T_g values between the batches cannot be explained by differences in molecular weight and methoxy-hydroxypropoxy substitution clearly indicates that there are batch specific interactions present that influences the T_g. As mentioned earlier, Viriden, Wittgren, Andersson, Abrahmsen-Alami, et al. (2009) and Viriden, Wittgren, Andersson, and Larsson (2009) have previously reported on batch specific interactions being present in solution for the batches in this study. The interac-

tions were proposed to derive from the heterogeneous distribution of the substituents. For batches of HPMC where the substituents are heterogeneously distributed there would be larger regions of unsubstituted glucose units and regions with more substituents than expected statistically. In large unsubstituted regions, the OH groups of the native glucose units would be more available for hydrogen bonding, due to less disrupted structure. As stated earlier, it is well known that hydrogen bonding contributes to increased T_g values. Native polysaccharides such as starch and in particular cellulose are known to exhibit T_g values higher than those reported for the HPMC batches in this study, as seen in the paper by Paes et al. (2010). For dry cellulose some reported T_g values are; 220 °C (Kargin, Kozlov, & Van, 1960), 253 °C (Goring, 1963) and 205 °C for ball milled cellulose (Paes et al., 2010). Therefore, an increased heterogeneity in the distribution of the substituents, allowing for more of the native interactions to remain, should result in an increase in T_g. Furthermore, it would be possible that regions of hydrophobic substituents interact somewhat stronger in heterogeneously substituted samples, as compared to samples with homogenous substitution pattern. This possibly increased the T_g even more.

Previously, the percent glucose liberated after enzyme hydrolysis has been taken as a measurement of the heterogeneity of the substituents in the batches, where a larger percent of liberated glucose is coherent with a more heterogeneous substitution pattern (Viriden et al., 2009a; Viriden, Wittgren, Andersson, Abrahmsen-Alami, et al., 2009; Viriden, Wittgren, Andersson, & Larsson, 2009). If there are interactions present that depend on the heterogeneity of the substituents and if those interactions do lead to higher T_g values, then the following order of the T_g values is expected from the percent glucose liberated after enzyme hydrolysis: $T_g^D < T_g^A < T_g^C < T_g^B$.

Indeed, the percent glucose liberated, taken to be a measurement of the substitution pattern, is the first of the investigated molecular characteristics that gives the correct order of the T_g values for the studied batches. Furthermore, when plotting the T_g versus the percent glucose liberated after enzyme hydrolysis a close to linear relationship is observed (Fig. 4). The curve in Fig. 4 does not extrapolate to zero in either axis, which is expected for two different reasons. First, even a sample with a close to homogenous distribution of the substituents should liberate some glucose due to structural reasons. Second, even a sample with a perfect homogenous distribution will have a rather high T_g. From the analysis of the dependence of T_g on the percent glucose liberated after enzyme hydrolysis, it is concluded that; increased heterogeneity with regard to the distribution of substituents leads to increased interactions.

When taking into account all of the above discussions on the dependence of T_g on molecular characteristics it is concluded that the dependences are highly complex. The molecular weight does not seem to influence the T_g to a large extent for the batches in this study, the total degree of substitution do seem to influence the T_g, and finally there is a strong linear correlation between the percent glucose liberated after enzyme hydrolysis and T_g. However, it needs to be pointed out that the percent liberated glucose after enzymatic hydrolysis will also have a negative dependence on the total degree of substitution, see the original work by Viriden, Wittgren, Andersson, Abrahmsen-Alami, et al. (2009). Thus, the percent glucose liberated after enzyme hydrolysis can be considered to account both for heterogeneity in the substitution pattern and also for the total degree of substitution. Nonetheless, the strong correlation between T_g and the percent liberated glucose after enzyme analysis is of great interest, especially as T_g can be so easily acquired using DMA on compacts.

3.4. Water vapour sorption analysis

After having established that there is a strong influence on T_g from the chemical heterogeneity of HPMC batches, and remembering that the heterogeneity also strongly influence the solution behaviour, swelling and polymer release from tablets. It was considered interesting to investigate if similar differences could also be seen in the water vapour sorption and plasticization. To study this batch A and B was chosen. This as they are have been previously characterised both with regard to solution behaviour (Viriden, Wittgren, Andersson, Abrahmsen-Alami, et al., 2009) and with regard to tablet swelling and polymer release (Viriden, Wittgren, & Larsson, 2009). Powder from the two batches was equilibrated at different RH and the mass was recorded.

The water sorption–desorption revealed that the water sorption at different RH was close to identical between the batches. Both batches exhibited increased water sorption at high RH, the sorption curves displaying a well known type II behaviour (Brunauer, Deming, Deming, & Teller, 1940), see Fig. 5. This phenomenon has previously been described for starch, and is explained by the fact that the plasticization by water causes an increased availability of polar groups to interact with the water molecules (Al-Muhtaseb, McMinn, & Magee, 2004; Perdomo et al., 2009). From the water vapour sorption analysis it is concluded that no significant differences could be detected in the water vapour sorption behaviour of the batches.

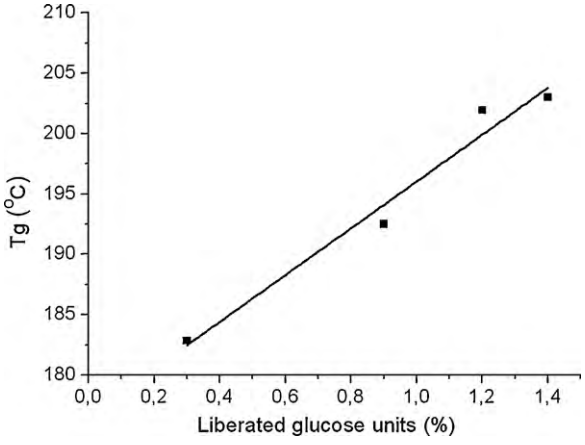

Fig. 4. The graph displays the T_g plotted versus the percent liberated glucose after enzyme hydrolysis.

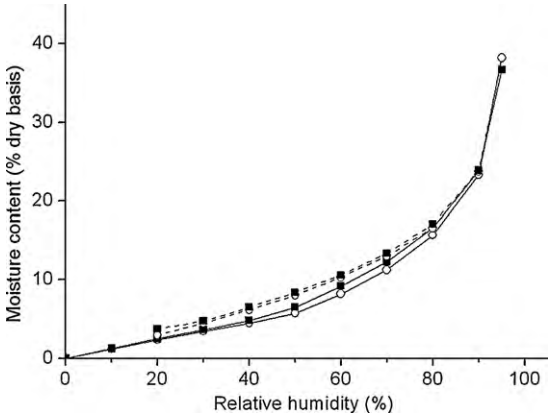

Fig. 5. The graph displays the moisture content of powder from batch A (○) and B (■) at different relative humidity, solid line indicates sorption and dashed line desorption.

3.5. Plasticization studies

To evaluate if there was a difference in the plasticizing effect of water between the two batches film samples were subjected to DMA under different RH and ambient temperature (about 26 °C), with a resolution in RH of ±1. The samples were first conditioned and analysed at 20% RH, followed by analysis at 90 and 95% RH. Finally the samples were analysed again at 20% RH. It was found from the increase in the loss factor tan(δ), that both batches became increasingly rubbery at 95% RH (results not shown). Furthermore, at 95% RH there was a small, but significant, difference in tan(δ) between samples from the two batches. Batch A had a slightly larger viscous character as compared to batch B at an RH of 95%. However, both samples had been plasticized to such an extent that they were stretched irreversibly under the small force applied in the DMA. Thus, if this deformation under applied stress is taken as a criterion for a polymer material being in the rubbery state, then it can be concluded that, at the temperature of the analysis, both batches went from glassy to rubbery state around 95% RH, and that batch A was more plasticized than batch B, which is in line with the results from the thermomechanical analysis.

4. Conclusion

In this study we have shown that batches of HPMC of the same pharmaceutical grade, with similar chemical composition, but with different degree of heterogeneity with regard to the distribution of the substituents along the polymer chains, display differences in their T_g. The difference in T_g values between batches is coherent with the degree of substitution and heterogeneity in the substituent pattern. This connection between the T_g and the heterogeneity has to our knowledge not been shown earlier for HPMC or other cellulose ethers. This knowledge of the T_g's dependence on the heterogeneity of the substituents should be of great importance as the heterogeneity is seldom analysed and since the T_g is a property of much importance in polymer materials.

Of much interest is that the T_g values of the studied batches had a strong linear dependence on the percent glucose liberated after enzyme hydrolysis, which in turn depends both on the degree of substitution and the heterogeneous distribution of the substituents. This is of great significance for controlled drug delivery applications as it is well known that the degree of substitution influences the pharmaceutical relevant properties of HPMC, and since the heterogeneity previously has been shown to have a profound impact on the gelling of and polymer release from HPMC tablets. The results presented in this paper suggest that the use of DMA to determine the glass transition temperature may be a good complement in characterising HPMC of similar chemical composition with regard to heterogeneity of the substituents. Furthermore, we report that DMA can be used in compression mode on compacts, without the use of any special sample holder. This should be a convenient and appealing way to analyse the glass transition of powder samples using a DMA apparatus, since it enables easy sample handling and analysis of samples as received from manufacturers. Interesting future prospects would be to investigate if the T_g can be used to provide complementary data to predict; solution, gelling and polymer release behaviour of certain polymers, perhaps even eliminating the need of some analyses that requires more effort than the described DMA method.

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