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CHEMICAL STRUCTURE AND GLASS TRANSITION TEMPERATURE OF NON-IONIC CELLULOSE ETHERS DSC, TMDSC®

Oscillatory rheometry study

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Abstract

Glass transitions of several non-ionic cellulose ethers differing in molecular mass and nature and amount of substituents were analyzed (as compressed probes) by differential scanning calorimetry (DSC), modulated temperature differential scanning calorimetry (TMDSC®), and oscillatory rheometry. In general, the low energy transitions accompanying the T_g of methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), and hydroxypropylcelluloses of low (L-HPC) or medium-high (HPC) degree of substitution were difficult to characterize using DSC. Non-reversing heat flow signals obtained in TMDSC experiments were more sensitive. However, the best resolution was obtained using oscillatory rheometry since these cellulose ethers undergo considerable changes in their storage and loss moduli when reaching the T_g. Oscillatory rheometry also appears as a useful technique to characterize the viscoelastic behavior and thermal stability of pharmaceutical tablets. T_g values followed the order HPC (105ºC)<HPMC (170–198ºC)<MC (184–197ºC)<L–HPC (220ºC). For HPMCs, the T_g increases as the methoxyl/hydroxypropoxyl content ratio decreases. The results indicate that T_g depends strongly on the structure of the cellulose ethers. In general, increasing the degree of substitution of cellulosic hydroxyls, the hydrogen bonding network of cellulose decreases (especially when the substituents cannot form hydrogen bonds) and, in consequence, T_g also decreases.

Keywords: glass transition, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC and L-HPC), modulated temperature differential scanning calorimetry (TMDSC), methylcellulose (MC), oscillatory rheometry

Introduction

The glass transition temperature (T_g) of an amorphous polymer is the temperature at which a change from a hard glassy form to a rubber-like plastic structure or viscous fluid occurs [1]. The glass transition is observed macroscopically by a change in the physical and mechanical properties of the material [2]. From a pharmaceutical point of view, the glass transition is a critical factor in processes such as compaction [3], drying and storage [4, 5], film formation during coating [2], thermal annealing [6], and water sorption and dissolution [7]. In addition, low molecular mass molecules (e.g. drugs) may act as plasticizers and modify the T_g significantly [8–10].

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Cellulose ethers are a class of semisynthetic polymers obtained from a chemical reaction of the hydroxyl groups at positions 2, 3 and/or 6 of anhydroglucose residues of cellulose. Their properties as excipients in drug dosage forms depend not only on the type of substituent(s), but also on the degree of substitution (DS, the average number of modified hydroxy groups per glucose residue) and the distribution of the substituents along the polymer chain [11]. T_g characterization of some cellulose ethers has been carried out mainly by differential scanning calorimetry (DSC) as powders [8] or films [12]. The glass transition is accompanied by an increase in heat capacity and, in many cases, a relaxation endotherm. However cellulose ethers usually show a glass transition of low intensity and the associated change in heat capacity is too small to be detected using a conventional DSC [13]. In these cases, modulated temperature differential scanning calorimetry (TMDSC®) presents important advantages. In TMDSC, a sinusoidal heating profile is overlaid on the conventional linear heating ramp. The sinusoidal modulation results in a fast instantaneous heating rate, which provides sensitivity, while the slow underlying heating rate used provides resolution [12]. The ability of TMDSC to divide the total heat flow into heat capacity and kinetic components (DSC only measures the total heat flow) permits the separation of overlapping phenomena and deconvolution of complex transitions, greater resolution without loss of sensitivity (signal-to-noise ratio at least double than in DSC), and greater ease of collection of heat capacity data [14–16]. In the particular case of cellulose ethers, McPhillips *et al.* [17] and Nyamweya and Hoag [12] have characterized the glass transitions of films made of hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) or methylcellulose (MC). No T_g was found for HPC films, while HPMC and MC films showed glass transitions at 150–190 and 191ºC, respectively.

Dynamic mechanical analysis (DMA), based on the application of a sinusoidal stress at a fixed frequency to the material while the temperature is varied, was also used to record the evolution of the mechanical moduli of films made of some cellulose polymers [13, 18]. The T_g values of cellulose ethers reported in literature show a considerable discrepancy depending on the variety of cellulose ether analyzed. Usually, the substitution pattern is unknown and the samples differ on molecular mass making it difficult to establish a relationship between structure and T_g. The solvent and way in which the films are prepared also condition intra- and intermolecular interactions and, in consequence, the T_g values [18].

Oscillatory rheometry has been recently adapted to the analysis of solid compacts. Although there are no references to its application to the pharmaceutical field yet, oscillatory rheometry seems to be a more versatile technique than DMA since it allows a complete characterization of the viscoelastic behavior of the material, not only as films but also as tablets of relatively great thickness. Applying oscillatory rheometry, the primary glass-rubber transition (α-transition) is characterized by a large decrease in the storage modulus (G') and a maximum in both the loss modulus (G'') and in the ratio of the loss to the storage moduli (tanδ) [19]. Secondary transitions (β- or γ-transitions) may also be detected in some polymeric materials [20, 21].

The aim of this study was to characterize the glass transitions that happen in tablets of various non-ionic cellulose ethers selected to cover a wide range of molecular mass and substitution patterns. Since these excipients are commonly used for tableting, it is clearly desirable to understand the influence of the structure of the polymer on the calorimetric and viscoelastic behavior of the tablets as the temperature changes. Therefore, applying DSC, TMDSC, and oscillatory rheometry, we intended to find a relationship between the nature and the degree of substitution and the glass transitions of the polymer.

Experimental

Materials

Methylcelluloses (MC) Methocel® Premium A4C, A15C, and A15LV, and hydroxypropyl methylcelluloses (HPMC) Methocel® Premium E4M, F4M, K4M, and K15M were from Dow Stade Gmbh (Germany). Low substituted hydroxypropylcelluloses (L-HPC) LH-20, LH-21, and LH-22 were supplied by Shin-Etsu Chemical (Japan). Medium and high substituted hydroxypropylcelluloses (HPC) Nisso® M (batches BJ, DC, and JD) and Nisso® H (batches BJ and JE) were from Nippon Soda (Japan). Table 1 summarizes the molecular mass and the substitution properties of each polymer [21].

Sample preparation

Rectangular probes (14×10 mm) of 1.5–2.0 mm thickness of each cellulose ether were prepared by direct compression in a Korsch Eco (Erweka, Germany) eccentric tableting machine using rectangular punches, and applying a compression force of 20500±500 N. For DSC and TMDSC studies, pieces of tablets were cut and used directly as samples.

DSC and TMDSC studies

Calorimetric characterization of cellulose ethers as powders and tablets was carried out, in duplicate, using a DSC Q100 (TA Instruments, New Castle, DE, USA) with a refrigerated cooling accessory (RCS) and modulated capability. Nitrogen was used as the purge gas at a flow rate of 50 mL min^{-1}. The calorimeter was calibrated for baseline using no pans, for cell constant and temperature using indium (melting point 156.61ºC, enthalpy of fusion 28.71 J g^{-1}), and for heat capacity using sapphire standards. All experiments were performed using non-hermetic aluminium pans, in which 5–10 mg samples were accurately weighed, and then just covered with the lid. The samples were loaded on an autosampler tray. Samples for DSC study were program-heated from 30 to 220ºC, then cooled to 0ºC, and finally heated again up to 220ºC, always at the rate of 20ºC min^{-1}. TMDSC experimental conditions were as follows: after equilibration at 40.0ºC, the temperature rises up to 260ºC, at 3 or 10ºC min^{-1}, using a modulation amplitude of ±1ºC every 100 s. The total heat flow signal was separated (applying the Fourier Transform algorithm; Universal Analysis 2000, v.3.3B, TA Instruments) into a heat capacity component (reversing heat flow) and a kinetic component (non-reversing heat flow), as shown in Eq. (1),

$$\frac{dQ}{dt} = C_p \frac{dT}{dt} + f(t,T) \tag{1}$$

where dQ/dt is the total heat flow, C_p is the heat capacity, dT/dt is the heating rate, and $f(t,T)$ represents the heat flow from events which are a function of time and absolute temperature (kinetic events) [14–16, 24]. T_g is reported as the midpoint of the glass transition.

Table 1 Some molecular and structural characteristics of the cellulose ethers studied

Polymer	Varieties	Average molecular mass	Methoxyl content/%	Hydroxypropoxyl content/%
MC[a]	A15LV	15 000	28-31	–
	A4C	41 000	28-31	–
	A15C	63 000	28-31	–
L-HPC[b]	LH-20	n.a.	–	13.2
	LH-21	n.a.	–	10.6
	LH-22	n.a.	–	7.5
HPC[b]	M-BJ	600 000	–	61.4
	M-DC	570 000	–	61.2
	M-JD	537 000	–	61.3
	H-BJ	1 070 000	–	60.9
	H-JE	1 130 000	–	60.9
HPMC[b]	E4M	95 000	29.3	8.4
	F4M	90 000	28.2	6.5
	K4M	84 000	22.9	8.3
	K15M	111 000	23.3	8.6

[a] data provided for the supplier;
[b] data taken from Alvarez-Lorenzo *et al.* [22]; n.a.: not available.

Oscillatory rheometry

The temperature dependence of the elastic and viscous moduli of cellulose ether tablets (G' and G'', respectively) and of tanδ ($=G''/G'$) was recorded in a Rheolyst AR1000N rheometer (TA Instruments, New Castle, DE, USA) equipped with an AR2500 data analyzer, an environmental test chamber and a solid torsion kit. The experiments were carried out in duplicate for an angular frequency of 1 rad s^{-1} by measuring these parameters while increasing the temperature from 25 to 220°C at 3°C min^{-1}.

Results and discussion

Table 2 summarizes the results obtained in determination of T_g for each cellulose ether. The discrepancies in T_g obtained using different techniques are related to the different physical parameters measured with each procedure [19]. Figure 1 shows the DSC scan of a HPMC E4M tablet, which was very similar to the other polymers. In all cases, the first scan shows an endotherm between 50 and 100ºC corresponding to the evaporation of the moisture content (around 1–3% measured by thermogravimetric analysis). During cooling, a small change in heat capacity was only observed in MCs and L-HPCs tablets around 124–127ºC. In the next heating run, in addition to this signal, some MCs presented another transition at higher temperature, which indicates that the product contains, owing to its synthesis procedure, macromolecules of markedly different molecular mass and/or crystallinity [22]. In the case of HPCs and HPMCs, only a change in the baseline was shown between 160 and 205ºC. In general, it was necessary to magnify greatly the scan to analyze the transitions. The DSC scans obtained for cellulose ether powders were similar to those recorded for the tablets, which indicates that compression did not modify the glass transitions of the polymer.

Table 2 Glass transition temperatures of tablets of the cellulose ethers studied, determined by DSC, MTDS and oscillatory rheometry

Polymer	Varieties	Transition values/°C		
		DSC	TMDSC	Oscillatory rheometry
MC[a]	A15LV	124	160	197
	A4C	124, 150	165	195
	A15C	124, 194	191	184
L-HPC	LH-20	120	127, 221	225
	LH-21	126	126, 220	225
	LH-22	126	126, 221	225
HPC	M-BJ	205	208	101, 210
	M-DC	205	211	102, 210
	M-JD	205	213	105, 210
	H-BJ	200	208	101, 210
	H-JE	205	211	105, 210
HPMC	E4M	163	151, 184	170
	F4M	173	180	178
	K4M	196	188	194
	K15M	198	187	198

In addition to the low sensitivity of DSC, the measurement of heat capacity by this technique requires three scans to avoid interferences from any residual moisture in the samples. This means that it is possible that changes in the integrity and the composition of the sample may have occurred during the first heating run, and the transitions observed in the following runs may be an artifact [12]. In contrast, TMDSC permits the separation of accompanying enthalpic events and a single sample run is enough to measure the change in heat capacity. The TMDSC conditions were chosen based on previous work which reported that long period times (100 s) and large modulation amplitudes (±1ºC) are recommended in order to obtain good accuracy and signal-to-noise ratios [14]. We also observed that a heating rate of 10ºC min^{-1} provides better sensitivity than 3ºC min^{-1} [22].

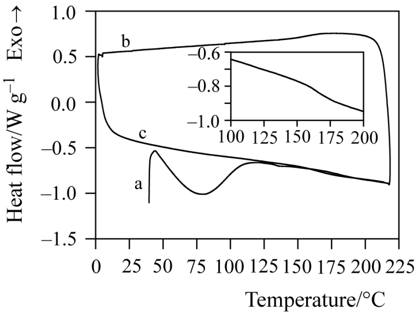

Fig. 1 DSC curves of HPMC E4M; a – first heating; b – cooling; c – second heating, insert: expanded third heating run

Figure 2 shows the TMDSC scans of MC A15C, HPC H-JE and HPMC F4M and K15M. For all cellulose ether tablets, the total heat flow shows a broad low temperature endotherm and a small discontinuity in the baseline between 160 and 220ºC, depending on the type of polymer. In the case of HPC, a clear endotherm is also shown around 210ºC. The glass transitions can be seen in the reversing heat flow signal (T_g data in Table 2). MC tablets showed a clear glass transition between 160 and 195ºC, the lowest T_g and energy associated to the process (~0.03 J g^{-1} ºC^{-1}) corresponding to the varieties with the lowest molecular mass. A similar influence of the molecular mass on the T_g was reported by Kararli *et al.* [13] for HPMC samples with molecular masses ranging between 6000 and 15000. T_g obtained for MC A15C

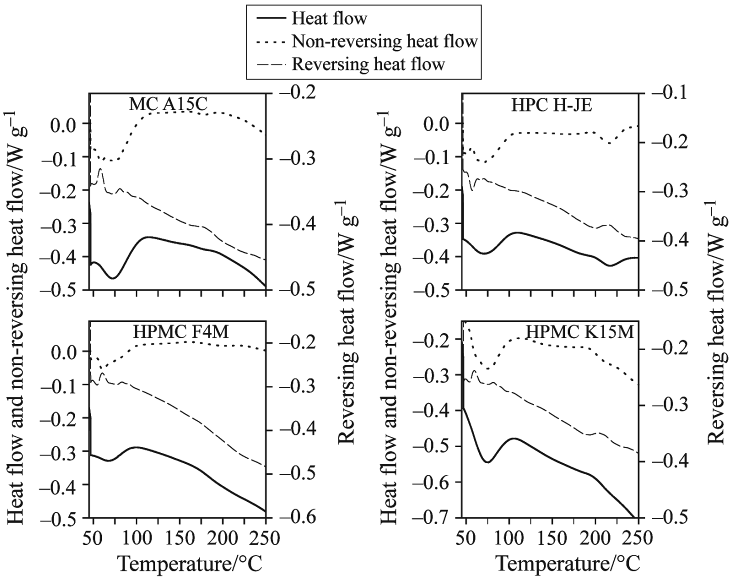

Fig. 2 TMDSC scans of MC A15C, HPC H-JE and HPMCs F4M and K15M compressed probes, showing separation of the response into reversing and non-reversing heat flow signals

(195ºC; ≈0.10 J g^{-1} ºC^{-1}) was similar to the value reported previously in the literature for MC varieties of high molecular mass [12].

L-HPC tablets presented TMDSC curves similar to the MC tablets, except that in two distinct transitions at 127 and 220ºC (Table 2) of similar energy values (≈0.03 J g^{-1} ºC^{-1}), were observed. The highest T_g resembles the typical glass transition of dry cellulose [1], which is undoubtedly due to the fact that L-HPCs present a low degree of substitution, retaining the initial cellulosic structure [11, 21]. The lower T_g may be related to the movement of the hydroxypropoxyl side chains [22].

The hydroxypropyl celluloses with a higher degree of substitution (HPCs) behaved in a totally different way, with an endothermic transition around 210ºC. Since HPCs can form liquid crystal phases and present a complex substitution pattern, it is not clear if the endothermic transition is due to a glass transition, the melting of the crystalline phase or a liquid crystal isotropic transition [12].

In the case of HPMC, important differences in T_g were observed depending on the methoxyl/hydroxypropoxyl content ratio. E4M and F4M samples showed a typical glass transition at temperatures lower than K4M and K15M. For these last two polymers, a small endotherm (less intense than for HPC samples) also appeared in the reversing heat flow.

In all cases, the different behavior of the polymers was seen more clearly applying oscillatory rheometry (Fig. 3), since the changes in the storage (G') and loss (G'') moduli were more intense than the calorimetric changes. L-HPC tablets presented the greatest stability *vs.* temperature. In contrast, for HPC tablets, both moduli gradually decreased above 100–110ºC, temperature at which δ (delta) showed a secondary

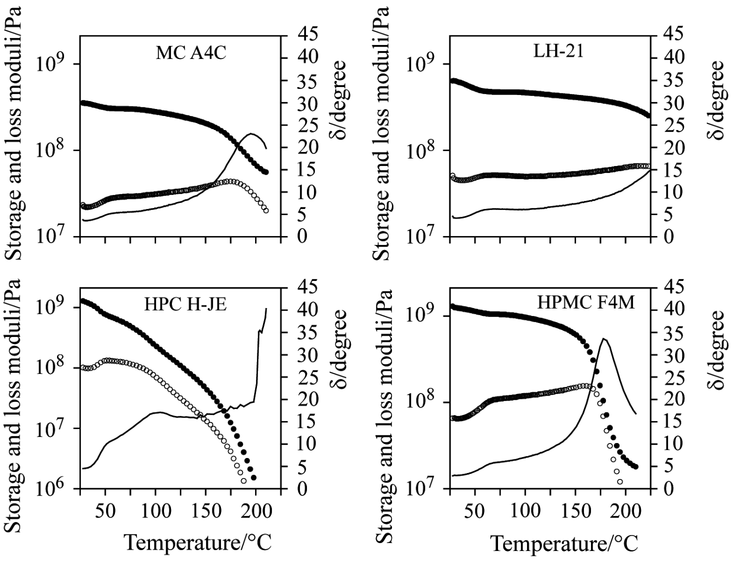

Fig. 3 Influence of the temperature on the storage moduli (G', solid symbols), loss moduli (G'', open symbols), and delta values (δ, line) of MC A4C, LH-21, HPC H-JE and HPMC F4M compressed probes, analyzed by oscillatory rheometry

maximum. Clear glass transitions were observed for MC and HPMC samples at around 170–198ºC, although the T_g differed significantly among varieties. Once again the importance of the methoxyl/hydroxypropoxyl content ratio on the T_g of HPMC tablets was clear (Fig. 4).

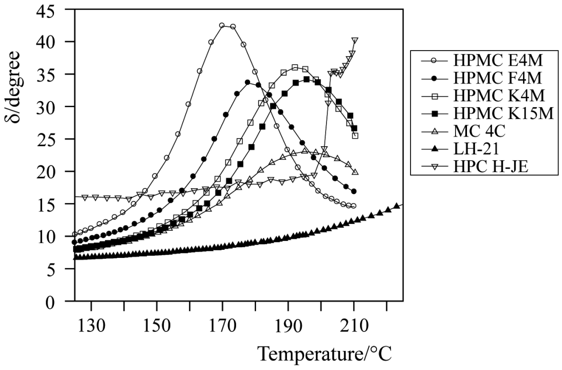

Fig. 4 Influence of cellulose ether variety on the glass transition temperatures (maximum delta values) observed using oscillatory rheometry

The results obtained may be explained as follows. The T_g is related to the onset of a certain degree of movement in the main chain and rotation of side segments. In the case of cellulose ethers, the primary glass-rubber transition (T_g) or α-transition is referred to the initiation of cooperative micro-Brownian motion of the main chain at high temperature, while secondary transitions correspond to the mobility of side groups (β-transition) or the rotation of end groups (γ-transition) at relatively lower temperatures. Pure cellulose shows a primary transition following DSC analysis at 220ºC [1]. In contrast, three glass transitions have recently been reported for cellulose microcrystalline at 132, 160, and 184ºC, applying TMDSC [22]. Cellulose microcrystalline is obtained by depolymerization of the amorphous regions of cellulose, increasing the number of end groups. The three glass transitions are attributed to the existence of regions of different molecular mass and crystallinity. In the case of cellulose ethers, during formation, alkyl side chains are bound to the hydroxyl groups of the cellulosic chain, and the microstructure of the polymer becomes more complex. Intra- and intermolecular interactions can occur between unsubtituted hydroxyl groups, ether oxygen groups, and hydroxyls introduced by the substituent groups. All this may condition the T_g of cellulose ethers. Specifically, introducing methyl substituents, as in MC, decreases the hydrogen bonds and increases the amorphous character of the polymer, which cause the α-transition (T_g around 160–191ºC) to appear at lower temperature than for pure cellulose. These data are consistent with the low T_g observed for ethylcellulose (131ºC), a cellulose substituted with ethyl groups that should disturb the hydrogen bonding network of cellulose even more than the methyl groups of MC [23]. In addition, the presence of methoxyl pendant groups may explain the secondary transition observed by DSC at 124ºC and as a shoulder in the rheogram at 60ºC.

On the other hand, introducing hydroxypropoxyl groups may increase the hydrogen bonding formation between substituents, raising T_g [5], and reduce the interactions of the unsubstituted primary hydroxyls of the cellulose chain at the time that the polymer becomes much more amorphous, lowering T_g [12, 13]. This explains why the samples with different degrees of substitution behave so differently: L-HPCs, with a smaller number of hydroxypropoxyl groups and higher crystallinity than HPCs [11, 21], present the highest T_g and thermal stability. Both HPCs and L-HPCs rheograms also present a shoulder at 60ºC, probably due to the movement of the hydroxypropoxyl substituents. It is interesting to notice in the rheogram of HPC tablets (Fig. 3, all batches showed the same behavior as HPC H-JE), the secondary maximum of δ that appears at 100–110ºC. Suto *et al.* [18] also observed a change in the dynamic mechanical properties of films of HPC at this temperature. This transition, which is only clearly evident on the viscoelastic properties of the material, may be related to the real α-transition of HPC. In contrast, the endotherm observed in the reversing heat flow and the loss of consistency registered in the rheogram above 200ºC may be due to the melting of the polymer.

HPMCs present a methoxyl content similar to MCs and a hydroxypropoxyl content close to L-HPCs. The samples with a higher total substitution content and higher methoxyl/hydroxypropoxyl ratio (E4M and F4M) showed the lowest T_g. As explained above, increasing methoxyl content decreases the hydrogen bonding ability of the polymer and, in consequence, the T_g. In contrast, the replacement of some methoxyl groups with hydroxypropoxyl groups may increase the intra- and inter-chain hydrogen bonds. Therefore, the highest T_g should correspond to the HPMC varieties with the lowest methoxyl/hydroxypropoxyl ratio (K4M and K15M), as can be seen in Fig. 4.

Conclusions

Considering the results obtained in this work together and the data reported in the literature, it is possible to state that increasing the degree of substitution, the T_g of non-ionic cellulose ether decreases; i.e. HPC<HPMC<MC<L-HPC. This effect is more intense in the case of substituents that cannot establish hydrogen bonds (methyl, ethyl). When different substituents are present on the cellulosic structure, such as in HPMC varieties, the ratio between those that cannot establish hydrogen bonds and those that do interact through hydrogen bonding determine the T_g value (HPMC E4M and F4M with greater methoxyl/hydroxypropoxyl ratios have a T_g 10–15ºC lower than HPMC K varieties). From a methodological point of view, oscillatory rheometry appears to be a particularly useful technique to characterize the low energy transitions of cellulose ethers that, nonetheless, produce substantial changes in the viscoelasticity of the polymer.

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