Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion - II: Cellulosic polymers.

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Received: January 23, 2014; *Accepted:* March 5, 2014

Original Article

ABSTRACT

The purpose of this study was to determine the thermal and viscoelastic properties of cellulosic polymers that may have potential for use in hot melt extrusion (HME). Cellulose ethers of different molecular weight (MW) with varied degrees of substitution and differences in substituted groups were analyzed using modulated differential scanning calorimetry (MDSC), thermogravimetric analysis (TGA) and oscillatory rheometry. The results indicated that the glass transition temperature (T_g) and viscoelastic characteristics of polymers appear to depend on their chain length, molecular weight (MW), and degree and type of substitutions in the main chain. In general, an increase in the chain length or MW increased T_g, as well as, the viscosity (HPMC, MW10000 < MW 25000 < MW 150000 Da). Additionally, substitutions with bulkier groups decreased both the T_g and the viscosity of the polymer. Most of the cellulosic polymers had high viscosity between their T_g and degradation temperature (T_d), and could not be extruded by themselves. The thermal properties in combination with polymer viscosity at different temperatures may assist formulating scientists in determining the processability when using HME.

KEY WORDS: Cellulose, HPMC, HPMC-AS, HPMCP, thermal properties, T_g, rheology, viscosity, polymers, hot melt extrusion

INTRODUCTION

There are numerous reports in the literature on the use of solid dispersion to enhance the dissolution of poorly water-soluble drugs (1, 2). One of the most viable processing techniques for the preparation of solid dispersions is hot melt extrusion (HME) as it has several advantages over traditional techniques (3). Amorphous solid dispersions by HME are prepared by melting the carrier and drug at a high temperature within the extrusion barrel (4, 5). HME has also been successfully employed for melt granulation (6, 7, 8). Despite its various ad-vantages, there are so far few products on the market using this technique, which is most likely due to the lack of full understanding of the processing parameters and concerns about physical and chemical stability (1, 2, 9, 10).

Cellulose is a polysaccharide consisting of linearly linked units of β(1→4) D-glucose units (11, 12). These linear polymer chains are arranged parallel to each other and are linked through hydrogen bonding. Because of the presence of a large number of hydroxyl and ether groups in the

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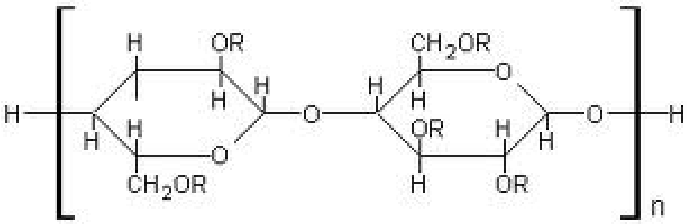
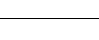
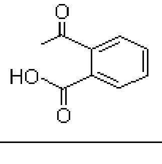
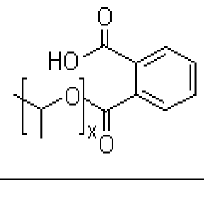
glucose units of polymer chains, celluloses have high intra- and inter-molecular hydrogen bonding. This results in crystallinity in native cellulose (40 to 90%) and also renders cellulose water insoluble despite being hydrophilic (12). Celluloses are converted to cellulose ethers by partially or fully reacting the hydroxyl groups of glucose units with different reagents. This also makes most cellulose derivatives water soluble since the remaining hydroxyl groups are accessible for hydration. Most cellulose derivatives are predominantly amorphous as the substituents cause a breakup of the hydrogen bonds that are responsible for crystallinity. Depending on the type of reagent used during derivatization, the physicochemical properties of these cellulose ethers vary and therefore may have application in a wide range of pharmaceutical processing techniques, including HME. Some of the common cellulose ethers and their substituent groups are listed in Table 1. Modified celluloses, such as methylcellulose (methoxy substituted cellulose) and hydroxypropyl cellulose (hydroxyl propoxy substitution), are soluble in cold water by providing free hydroxyl groups accessible for hydration and hydrogen–bond formation with water (13). Also, the aliphatic hydroxyl groups present in the side chains can form hydrogen bonds with proton donating moieties of APIs, which stabilizes the APIs in an amorphous state in solid dispersions (14, 15). Substitution with a bulkier water-insoluble group such as ethoxide (–OC_2H_5) in ethylcellulose renders the celluloses water-insoluble (13).

Table 1 Chemical structures of cellulose derivatives

GENERAL STRUCTURE OF CELLULOSE ETHERS (16)



CHEMICAL NAME	SUBSTITUENT (R)
Non-ionic cellulose ethers	
Methylcellulose, MC	R= -H, -CH_3
Ethylcellulose, EC	R= -H, -C_2H_5
Hydroxypropyl cellulose, HPC	R= - H, -$CH_2CH(OH)CH_3$
Hydroxypropyl methylcellulose, HPMC	R= -H , -CH_3, -$CH_2CH(OH)CH_3$
Ionic cellulose ethers	
Hydroxypropyl methylcellulose acetate-succinate , HPMC-AS	R= -H , -CH_3, -$COCH_3$, -$CH_2CH(OH)CH_3$ -$CH_2CH(CH_3)OCOCH_3$ -$CH_2CH(CH_3)OCOCH_2CH_2COOH$
Hydroxypropyl methylcellulose phthalate, HPMCP	R= -H , -CH_3,  ,  , 

Methylcellulose has been used together with water-insoluble ethylcellulose to increase the dissolution rate of ketoprofen in solid dispersions prepared by melt extrusion at 150°C (17). Low molecular weight HPMC (5 cps) was used to improve the physical stability, as well as, promote dissolution (18,19). Like methylcellulose, the hydroxypropoxyl group present in HPMC is capable of forming hydrogen bonds with APIs. Low molecular weight cellulosic polymers can be used as binders in melt granulation, whereas high viscosity grades have been extensively used as carriers in matrix tablets and solid dispersions (7, 19, 20). It stabilizes the amorphous drug in the formulation, increasing drug release due to its hydrophilic nature and thus aids drug supersaturation during dissolution (21,22). Modified HPMCs, such as hydroxypropyl methylcellulose acetate-succinate (HPMC-AS) and hydroxypropyl methylcellulose phthalate (HPMCP), provide an added advantage of an enteric property due to the presence of acetyl, succinoyl and phthaloyl substituents, respectively. HPMC-AS has been successfully used to prepare solid dispersions and have superior anti-crystallization effect when compared to other cellulosic and vinylpyrrolidone polymers (23–25). However, it is prudent to be cautious since cellulosic polymers may degrade at the high processing temperatures necessary for HME by dissociating the side chains and the formation of volatile materials. Under extreme processing conditions, there could also be cross-linking of polymers resulting in a decrease in the drug dissolution rate (26). For these reasons, HPMC-AS should not be extruded at a temperature greater than 140°C (24). At higher temperatures, it releases free acetic acid and succinic acid, which could react with the drug or other excipients, such as lactose, that contain free -OH groups (27). Water-insoluble cellulose ethers, such as ethyl cellulose (EC), are commonly used in modified release dosage forms. They can be combined with a hydrophilic polymer to obtain a desired drug release profile (28).

Although the application of cellulosic polymers in HME has been reported, there have been no systematic studies carried out comparing their physicochemical properties nor determining criteria for their selection for melt extrusion. Polymers for solid dispersion are usually selected on the basis of their miscibility with a drug, capability of preventing drug crystallization, and ability to increase or modify drug dissolution. Additionally, for melt extrusion, polymers with too high a T_g value are not suitable because of the high processing temperature, which may degrade the polymer, drug or both. The T_g and the T_d of polymers should be sufficiently far apart to ensure thermal stability during extrusion.

The objective of this study was to increase the understanding of the thermal and rheological properties of cellulosic polymers. Thermal properties, such as T_g and T_d, provide information about the thermal conditions required for melt extrusion. The viscosity of the polymers, as a function of temperature, was studied to provide information regarding their processability and, combined with the thermal data, establish an optimum processing temperature range for hot melt extrusion.

MATERIALS

A detailed description of the polymers used is provided in Table 1. Pharmacoat® 606 (HPMC 6 cps), HPMC-AS (Shin-Etsu AQOAT® AS-MG) and HPMCP (HP-50 and HP-55) were donated by Shin-Etsu Chemicals, Tokyo, Japan. HPMC (Methocel™ K100LV and K100M) and methylcellulose (Methocel® A15LV) were purchased from The Dow chemical Company, Michigan , USA. Klucel® LF (HPC) was donated by Ashland Inc., DE, USA and ethylcellulose (Ethocel® 4P, 7P and 10P) was donated by Colorcon, PA, USA.

METHODS

Powder XRD

A powder X-ray diffractometer (Shimadzu 6000, Kyoto, Japan), pre-calibrated by the manufacturer, was used to obtain the X-ray diffraction patterns at room temperature using the following process parameters: a Ni filtered monochromatic CuKa radiation source operated at 60 kV and 55 mA, step scanning rate of 2°θ/min and step size of 0.02°over the range of 10°-60°. The samples were prepared into thin films by the "sideways filling method" onto a glass sample holder.

Thermogravimetric Analysis (TGA)

Approximately 4-6 mg of each polymer was analyzed using a thermogravimetric analyzer, TGA Q50 (TA Instruments, DE, USA). The samples were heated from 25 to 300°C at a rate of 5°C/min under a continuous nitrogen flow of 60 ml/min. The first decrease in weight at between 25 and 100°C was considered due to moisture loss. The start of the second weight loss in a thermal scan was considered the onset of degradation.

Modulated Differential Scanning Calorimetry (MDSC)

Conventional modulated DSC studies were carried out using a MDSC Q200 (TA instruments, DE, USA) under a constant nitrogen purge of 50 ml/min. The instrument was calibrated using an indium standard for heat flow and temperature and, a sapphire standard for heat capacity. Approximately 3-6 mg of polymer was loaded into an aluminum pan, which was then closed and crimped with an aluminum lid. The sample was equilibrated at 25°C for 3 minutes, followed by heating the sample from 25 to 250°C at a rate of 3°C/min with a modulation rate of 1°C/min during the entire sequence. A step change in the reversing heat flow signal was taken as T_g and an endothermic peak was taken as the melting temperature.

Rheological studies

Detailed methods for the rheological analysis and the rheological parameters measured, such as complex viscosity (η*), the loss tangent (tan δ), storage modulus (G′) and loss modulus (G″), have been discussed previously (29). Briefly, 1 gram of polymer was compressed into a slug of 25 mm diameter using a Carver press at 5000 pounds pressure for 5 seconds. A hybrid rheometer with an oven heating assembly (Discovery DHR-2, TA instruments, DE, USA) was used for the analysis. The polymer slug was placed between the parallel plates and a dynamic oscillation temperature sweep was performed from high to low or low to high temperature at 5°C/min. The highest temperature point used for the study was at least 10°C below the T_d of the polymers. The angular frequency of oscillation was 0.1 rad/sec with 0.5 % of applied strain. The crossover temperature (tan δ =1) denotes the transformation from glassy to rubbery state. The temperature range corresponding to the complex viscosity of 1000-10000 Pa.s was taken as the possible temperature range at which pure polymers can be extruded as explained previously in more detail (29).

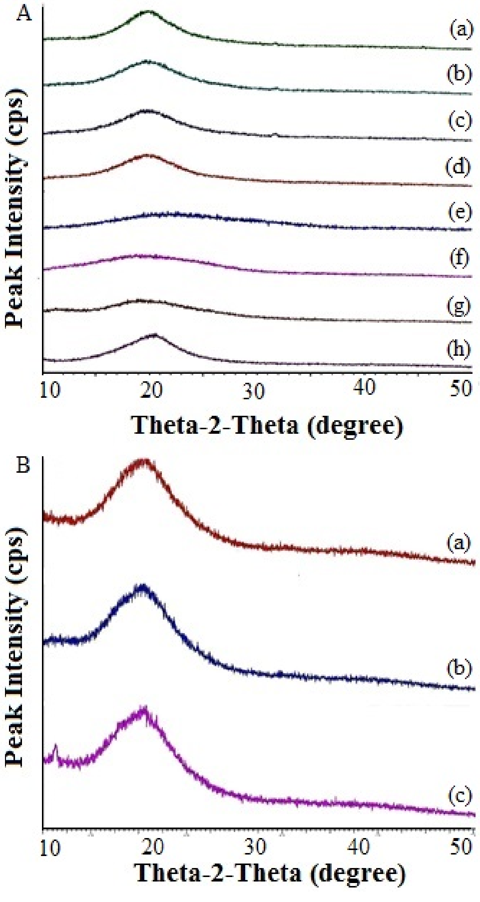


Figure 1 Powder XRD patterns of A) water-soluble cellulosic polymers (a) Methylcellulose, (b) HPMC 6 cps, (c) HPMC 100 cps, (d) HPMC 100000 cps, (e) HPMCP HP-50, (f) HPMCP HP-55, (g) HPMC-AS 3 cps, (h) HPC and B) water-insoluble cellulosic polymers (a) EC 4 cps, (b) EC 7 cps and (c) EC 10 cps.

Table 2 Summary of thermal and rheological properties and extrudable temperature ranges of cellulosic polymers

CHEMICAL NAME	TRADE NAME	T_g/T_m (°C)	CROSSOVER TEMPERATURE (°C) (Tan δ=1)	T_d (°C)	% MOISTURE CONTENT	EXTRUDABLE T RANGE (1000-10,000 Pa.s)
Water Soluble Cellulose Ethers						
Hydroxypropyl methylcellulose, 6 cps (MW – 10000)	Pharmacoat® 606	139	*	244	< 2.0	**
Hydroxypropyl methylcellulose, 100 cps (MW – 25000)	Methocel™ K100LV	147, 168	*	259	< 0.5	**
Hydroxypropyl methylcellulose, 100000 cps (MW – 150000)	Methocel™ K100M	96, 173	*	259	< 1.5	**
Hydroxypropyl methylcellulose acetate-succinate 3cps (MW – 18000)	Shin-etsu AQOAT® MF	122	132	204	< 0.5	**
Hydroxypropyl methylcellulose phthalate, 40cps (MW – 45600)	HP-55	147	162	194	< 1.0	**
Hydroxypropyl methylcellulose phthalate, 55cps (MW – 37900)	HP-50	143	148	199	< 1.0	**
Methylcellulose 15 cps (MW – 14000)	Methocel™ A 15LV	175	*	247	< 1.5	**
Hydroxypropyl cellulose (MW – 95000)	Klucel® LF	111	190	227	< 0.2	170-200
Water Insoluble Cellulose Ether						
Ethylcellulose 4 cps	Ethocel® 4P	128, 168	184	200	< 1.0	184-198
Ethylcellulose 7 cps	Ethocel® 7P	128, 168	192	205	< 0.07	192-200
Ethylcellulose 10 cps	Ethocel® 10P	132, 172	194	205	< 0.001	195-200

* Within the experimental temperature range, the storage modulus and loss modulus did not intercept.

** Within the experimental temperature range, the viscosity values for the polymers were more than 10,000 Pa.s, which were higher than the extrudable viscosity.

RESULTS AND DISCUSSION

Powder XRD

Powder X-ray diffraction patterns for various cellulose ethers are shown in Figure 1. Celluloses exist as semi-crystalline polymers and their semi-synthetic derivatives may retain some degree of crystallinity (30, 31). The XRD patterns, however, suggest that all cellulosic polymers used in the present study were amorphous because of the absence of any defined peaks between $10° \leq 2\theta \leq 60°$. All polymers exhibited characteristic broad halos at around $2\theta = 20°$, which was similar to the amorphous region in native celluloses that exhibited a diffraction halo at 18° (11).

Modulated Differential Scanning Calorimetry (MDSC)

The thermal events associated with phase transitions were studied using MDSC (Figure 2) and the T_g values are listed in Table 2. The T_g and T_m can be observed in the reversing flow signals in the MDSC heating curve. MDSC scans of all water-soluble ethers did not exhibit any endotherm (Figure 2A), which confirms the amorphous nature of these polymers. However, in case of ethylcelluloses, shallow endotherms characteristic of crystalline materials were observed (Figure 2B), though no crystalline peaks were observed in powder XRD. Methylcellulose (MC) showed the highest T_g (~175°C) among all cellulosic polymers tested despite its low MW of about 14000 Da In contrast, HPMC 6cps with the comparable MW of 10000 Da had a much lower T_g of 139 °C. This could be due to structural differences between MC and HPMC. Although they have similar methoxy content (~ 28-30%), HPMC has bulkier hydroxyl propoxy groups, and consequently has shorter chain length (considering that both have similar MW). Similarly, despite higher MW (~95000 Da), HPC had a low T_g at approximately 111°C, which could be due to the presence of a 66% hydroxyl propoxy group substitution rather than methyl groups. Additionally, a bulkier substituent results in a greater fractional free volume due to the expansion of intermolecular distance. This causes disruption in the hydrogen bonding capacity of

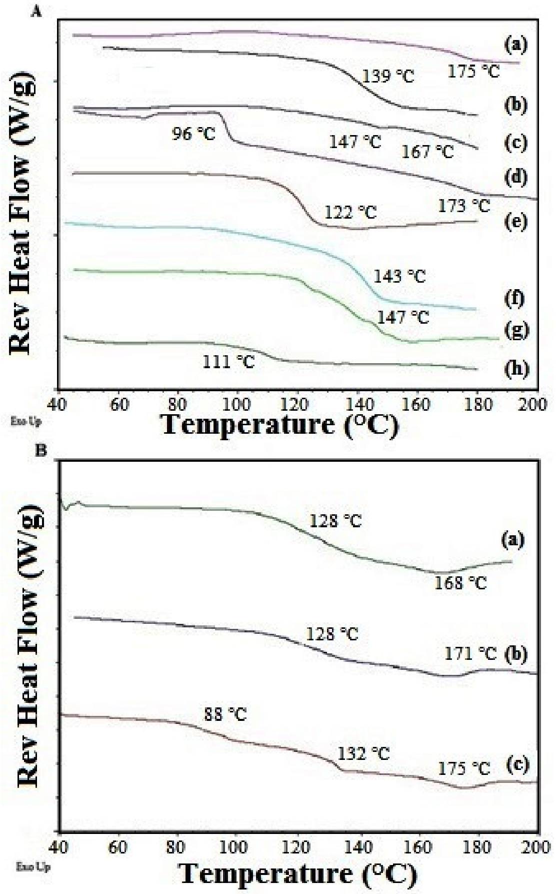


Figure 2 MDSC heating curves of A) water-soluble cellulosic polymers (a) MC, (b) HPMC 6 cps, (c) HPMC 100 cps, (d) HPMC 100000 cps, (e) HPMC-AS 3 cps, (f) HPMCP HP-50, (g) HPMCP HP-55, (h) HPC and B) water-insoluble cellulosic polymers (a) EC 4 cps, (b) EC 7 cps and (c) EC 10 cps.

the hydroxyl groups between two polymer chains and thus results in decreases in T_g (32). The MW and chain length showed definite impact on the T_g as HPMC 100000 cps (MW ~ 150000 Da) had a T_g value of of ~173°C, followed by HPMC 100 cps (MW ~25000 Da) with a T_g value of ~168 °C and HPMC, 6 cps (MW ~10000 Da) with a T_g value of ~139 °C. HPMC 100 cps and 100000 cps showed secondary transitions at 147°C and 96°C, respectively.

It is suggested that these secondary transitions may be due to various factors, including segmental motion of polysaccharide chains attached to glucose units via glucosidic bonds (β-relaxation), movements of the sorbed water content in the cellulosic polymer (β wet-relaxation), or motion of side groups attached to glucose units via glucosidic bonds (ϒ-relaxation) (33). HPMC-AS (MW ~ 18000 Da), HPMCP (HP50, MW ~ 37900 Da) and HPMCP (HP55, MW ~ 45600 Da) had T_g values of 122°C, 143°C and 147°C, respectively. The T_g values of the different grades of EC (4 cps, 7 cps, and 10 cps) were in the temperature range of 127 to 132°C (Figure 2B), which agrees with the values reported in the literature (34). The MDSC scans also showed shallow endotherms between 170 and 180°C, which could be crystalline melting peaks (34). The lower T_g of EC compared to MC could be due to their structural differences since EC contains 48-50% of bulky hydrophobic ethoxy substitution on the parent cellulose backbone compared to the 30% smaller methoxy group substitution in MC. The bulkier and hydrophobic ethoxy groups considerably disrupts H-bonding compared to MC (35).

Thermogravimetric analysis (TGA)

Thermogravimetric analysis was performed for all polymers to measure the residual moisture content and degradation temperature. Table 2 shows that all water soluble cellulosic ethers contained < 2% moisture and ethylcellulose contains < 0.1% moisture. Thermal degradation of a few cellulosic ethers have been reported in literature at approximately 370-380°C, where 80% of weight loss was observed (36). However, HPMC and MC started to show a change in color (browning) at a temperature of approximately 240-250°C even though the weight loss at this temperature was less than 10% (36). As determined by weight loss in TGA, all non-ionic celluloses in this study were stable up to 240°C, except for HPC and EC which started degrading around 200°C (Table 2). The ionic cellulose ethers (HPMC-AS and HPMCP) started to degrade at a temperature of approximately 190 to 200°C. The degradation temperature should, therefore, be carefully considered in conjunction with T_g and melt viscosity when setting up processing temperatures for melt extrudates.

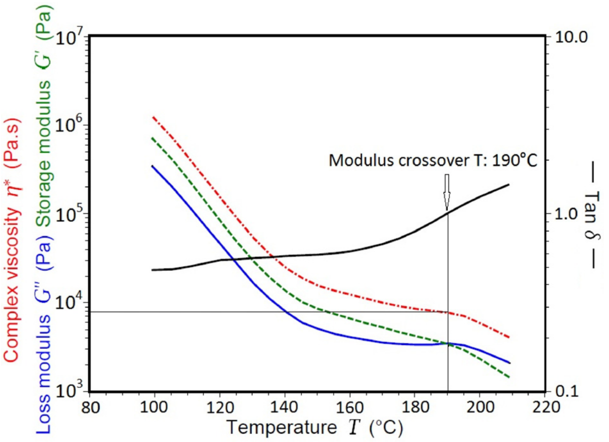


Figure 3 Influence of temperature on the (a) complex viscosity, (b) storage moduli (G′), (c) loss moduli (G″**)** , (d) tan delta lines (δ) and indication of cross over temperature (tan δ=1) of HPC analyzed by oscillatory rheometry.

Viscoelastic Properties

The application of oscillatory rheometry for one of the polymers, HPC, is illustrated in Figure 3. With the increase in temperature, storage modulus (G´), loss modulus (G″) and complex viscosity (η*) decreased. The crossover temperature (tan δ ~ 1) was observed at 190°C, almost 80 °C greater than its T_g. Above the crossover temperature, G´ was greater than G″, whereas below the crossover temperature G″ was greater than G´. This is because the polymer softens and behaves more fluid-like, losing its elastic property with increasing temperature. The results show that HPC was extremely stiff at T_g (viscosity ~ 500000 Pa.s) and thus cannot be extruded as the extrudable viscosity range is between 1000 to 10000 Pa.s (29). However, at the crossover temperature the complex viscosity was around 8000 Pa.s, which was within the extrudable range. The temperatures corresponding to the viscosity of 10000 and 1000 Pa.s were 170 and 200°C, respectively, and, therefore, the extrudable temperature range for HPC was taken to be from 170 to 200°C.

Figures 4A and 4B show the complex viscosity of water-soluble and water-insoluble cellulosic polymers, respectively, as a function of temperature. The appearance of polymer slugs at high temperature was carefully monitored to avoid any apparent sign of polymer degradation. The crossover temperatures of all polymers tested were above T_g, and in some cases not within the experimental temperature range (< 200°C). All polymers tested showed a decrease in melt viscosity with an increase in temperature. Rheological parameters of different cellulosic polymers are listed in Table 2. All polymers tested showed very high viscosity (>10000 Pa.s.) around their T_g. Significant differences between polymers were observed, since the polymers vary with respect to their MW and chain length. At high temperature, the polymer chains disentangle and arrange linearly, thereby facilitating flow and decrease in viscosity. Polymers with longer chain length have a higher degree of chain entanglement and thus higher viscosity. Similar to T_g, an increase in viscosity was observed with an

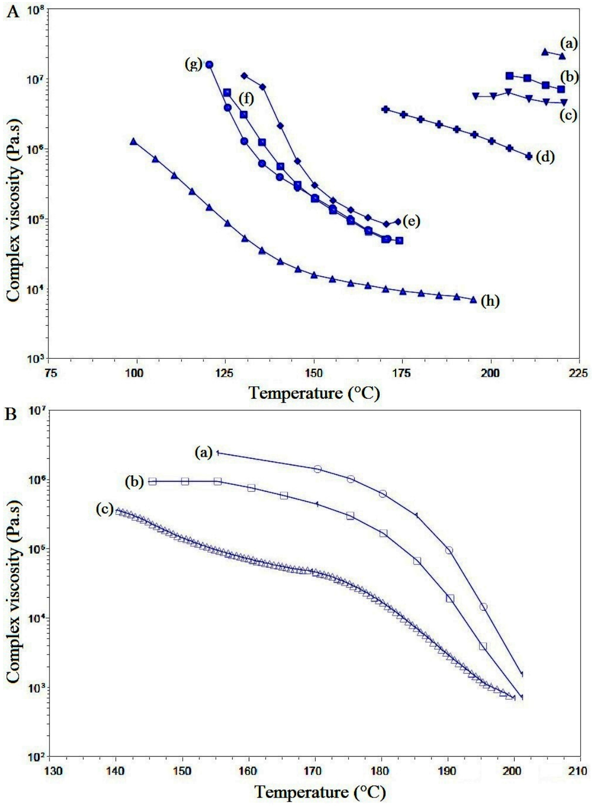


Figure 4 Complex viscosity of cellulose ethers as function of temperature: A) water-soluble cellulosic polymers (a) Methylcellulose, (b) HPMC 100000 cps, (c) HPMC 100 cps, (d) HPMC 6 cps, (e) HPMCP HP-50, (f) HPMCP/HP-55, (g) HPMC-AS, (h) HPC, and B) water-insoluble cellulosic polymers (a) EC 10 cps, (b) EC 7 cps and (c) EC 4 cps.

increase in the chain length and MW of HPMC (MW10000 < MW 25000 < MW 150000 Da). A similar effect of MW was also seen for ethylcellulose (EC 4 cps < EC 7 cps < EC 10 cps).

In addition, the type of substitution had a considerable influence on the viscosity. Methoxy substituted cellulose ethers (MC, HPMC and their derivatives) have considerably higher viscosity and crossover temperature compared to hydroxyl propoxy or ethoxy substitution. HPC (hydroxyl propoxy substitution) have much lower viscosity compared to HPMC 6 cps, HPMC 100 cps, as well as, HPMCP and HPMCAS (with both hydroxypropoxy and methoxy substitution) even though HPC has higher MW than HPMCs. As these polymers do not soften even at their T_d, they are not suitable for melt extrusion by themselves. Plasticizers are recommended to be used with these polymers as they can bring down the processing temperatures of the polymers. Prodduturi *et al.* (37) used 15 to 55%w/w polyethylene oxide (PEO) together with HPC to enable melt extrusion at 140°C. The formulation also contained 10% clotrimazole. It is possible that both the PEO and the drug served as plasticizers in the formulation. A similar approach may be taken if one intends to use MC, HPMC and its derivatives as polymers in melt extrusion of drug formulations.

CONCLUSION

Powder XRD and MDSC confirmed the amorphous nature of the polymers with the exception of ethylcellulose, which MDSC analyses showed were partially crystalline in nature. The MW and chemical structure of polymers had a considerable effect on their T_g and viscosity. An increase in MW or chain length invariably increased the T_g and melt viscosity (HPMC 100000 cps > HPMC 100 cps > HPMC 6 cps). Other than chain length, the degree and the type of substitution, influenced the thermal and viscoelastic properties of the polymers. Even with polymers with similar MWs, changes in the structure or substituted groups had a major impact on their thermal and viscoelastic properties. An increase in the degree of substitution caused an increase in hydrogen bonding within the polymeric chains that increased their T_g. The transition temperature ($\tan \delta = 1$) of all polymers were above their T_g. Moreover, most celluloses such as MC, HPMC, and their derivatives did not soften enough between T_g and T_d to enable their melt extrusion by themselves. It is possible that they may be extruded if appropriate plasticizers are used. The results of the present investigation demonstrate that the thermal properties were not sufficient to identify processing temperatures of cellulosic polymers, but the viscoelastic properties should also be evaluated to predict the extrudability and stability of polymers in HME.

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