Research paper

Dynamic mechanical thermal analysis of hypromellose 2910 free films

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ABSTRACT

It is common practice to coat oral solid dosage forms with polymeric materials for controlled release purposes or for practical and aesthetic reasons. Good knowledge of thermo-mechanical film properties or their variation as a function of polymer grade, type and amount of additives or preparation method is of prime importance in developing solid dosage forms. This work focused on the dynamic mechanical thermal characteristics of free films of hypromellose 2910 (also known as HPMC), prepared using three grades of this polymer from two different manufacturers, in order to assess whether polymer chain length or origin affects the mechanical or thermo-mechanical properties of the final films. Hypromellose free films were obtained by casting their aqueous solutions prepared at a specific concentrations in order to obtain the same viscosity for each. The films were stored at room temperature until dried and then examined using a dynamic mechanical analyser. The results of the frequency scans showed no significant differences in the mechanical moduli E' and E'' of the different samples when analysed at room temperature; however, the grade of the polymer affected material transitions during the heating process. Glass transition temperature, apparent activation energy and fragility parameters depended on polymer chain length, while the material brand showed little impact on film performance.

1. Introduction

Most of the oral solid dosage forms currently available on the market are coated with polymeric materials, making the coating procedure a crucial step in the manufacturing process. Coating films are used for several purposes, such as modifying release, affording gastroprotection, protecting tablets from environmental agents, masking unpleasant taste or just enhancing product aesthetics.

The physical and mechanical properties of polymeric films are fundamental for their performance. The release properties and the integrity of the final dosage forms during packaging, storing and shipping are all issues strongly influenced by the physical and mechanical features of the polymeric coating.

There are many papers in the literature on the mechanical properties of free films and their relation to polymer type [1–4], quantity and quality of additives [1,2,5–8], preparation methods or drying techniques [1,4,9]. Most of the papers deal with measuring the mechanical properties using the tensile tester and classical tests such as indentation, stress-strain, puncturing or transient mechanical tests (creep or stress relaxation). A detailed description of these kinds of tests for free film characterisation is offered in reviews by Aulton [10] and Felton et al. [11].

A very powerful alternative to traditional methods is dynamic mechanical thermal analysis (TDMA or DMA). This technique applies an oscillating stimulus (load or deformation) to a sample and analyses the response of the material. From the raw data, mechanical parameters such as storage modulus (E'), loss modulus (E'') and damping (the tangent of the phase angle tan d) can be determined and used to characterise the material properties. DMA can work scanning temperature, the amplitude or frequency of the stimulus or simply its extent [12]. Although DMA is an essential approach in many scientific areas involving materials characterisation, it is still largely underused in the pharmaceutical field. Up to now, DMA has been used in the analysis of film viscoelasticity and temperature-induced transitions [13–16], in the characterisation of the mechanical properties of pellets [17,18] or in the measurement of glass transition temperatures of powdered materials [19,20].

Hypromellose (formerly known as hydroxypropylmethylcellulose, HPMC) 2910 represents one of the more widespread polymer in pharmaceutical film coating, used mainly for aesthetic and protective reasons. Despite its wide use in the last 20–30 years as a polymer coating, there is still a lack of information concerning the film properties compared to those of the powder form.

Thus, aim of this work is to perform a complete thermo-dynamic-mechanical analysis of hypromellose 2910 free films, taking into account several grades available by the two main world manufacturers.

A deep knowledge of films mechanical and thermal properties, together with its variation according to the polymer length, is

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crucial in order to better formulate coating system used for solid oral dosage forms or any other products requiring the use of this polymeric films.

2. Materials and methods

2.1. Materials

Three different grades of hypromellose 2910 were selected in order to cover the entire range of viscosity types (or molecular weight) available from the two major suppliers. Methocel E6 premium LV, Methocel E15 premium LV and Methocel E50 premium LV (Colorcon, Dartford England) were supplied by Colorcon S.r.l. (Gallarate, Italy), while Pharmacoat 606, Pharamacoat 615 and Metolose 60 SH 50 (Shin-Etsu Chemical Co., LTD, Tokyo, Japan) were supplied by Seppic Italia Srl (Milan, Italy). The physico-chemical properties of the polymers are summarised in Table 1.

2.2. Preparation of polymer solutions

All the hypromellose solutions were prepared using the 'hot/cold' technique [23], by dispersing the polymer in one-third of the required amount of hot water (80 °C), then adding the remaining amount of cold water, under magnetic stirring until a clear viscous solution was obtained. All the solutions were left at 5 °C for at least 24 h before being analysed.

Solutions were prepared in the concentration range 2–10% w/w for each hypromellose viscosity type.

2.3. Flow curves of the solutions

Flow curves were determined with a controlled stress rheometer (StressTech, Reologica) using steel cone–plate geometry (C40/4). Shear stress was increased from 0.01 to 50 Pa and the corresponding shear rate measured, at a constant temperature of 20 °C.

Each sample was analysed in triplicate.

2.4. Preparation of the free films

Free films were obtained by casting aqueous hypromellose solutions at a suitable concentration (determined by viscosity analysis). For each viscosity grade, a different amount of solution was cast on a glass surface, in order to obtain a dry polymeric disc of equal weight and thickness (280 μm ± 5%). The discs were dried on a glass surface at ambient conditions until no decrease of weight was recorded. Once the discs were dried, they were removed from the glass surface and cut into regular rectangular samples (9.5 × 20 mm) using a guillotine cutter specifically modified for this purpose.

2.5. Thermogravimetric analysis of free films

The real water content of samples was determined by thermogravimetric analysis using an STA 6000 (Perkin Elmer, USA). For each viscosity and brand type, approximately 5–20 mg of samples were placed in aluminium crucibles and the weight loss analysed from 25 to 250 °C at a rate of 10 °C/min under nitrogen atmosphere.

2.6. Dynamic mechanical analysis of free films

The thermo-mechanical properties of the free films were analysed using a DMA 8000 (Perkin Elmer, USA) equipped with a closed furnace. All the tests were performed in bending mode, using dual cantilever geometry. All the free films were analysed using the following tests:

- Strain sweep: This test determines the linear viscoelastic region (LVR) of the samples, and therefore provides information for choosing the strain value to use in the other tests. The test was performed at 25 °C and at a constant frequency of 1 Hz, increasing the deformation amplitude from 1 to 100 μm.
- Frequency sweep: The test highlights the time-dependent behaviour of the samples under study. This analysis was performed at constant temperature (25 °C) by applying a fixed deformation amplitude (within the LVR) and increasing the frequency from 0.1 to 100 Hz.
- Temperature sweep: This test allows the study of the temperature-dependent behaviour of the samples and the analysis of possible temperature-dependent transitions such as melting, glass transitions (Tg or $T\alpha$) or sub-Tg transitions ($T\beta$ and $T\gamma$) [24]. The tests were carried out by applying a constant deformation amplitude (within the LVR) and increasing the temperature from 25 to 200 °C at a scanning rate of 3 °C/min. All the tests were performed in multifrequency mode (1, 2.5, 5 and 10 Hz), in order to highlight the time dependency of the transitions.

All the samples were analysed in triplicate.

3. Results and discussion

3.1. Viscosity of polymer solutions

The shear stress/shear rate curves obtained by the rheometer were analysed by the well-known power law equation:

$$\sigma = k\dot{\gamma}^n \tag{1}$$

where σ is the shear stress, $\dot{\gamma}$ the shear rate, k the consistency index and n the power law index.

The power law equation is an easy rheological model able to describe the flow of Newtonian and many non-Newtonian systems. The consistency index k, also called power law viscosity, is related to the system viscosity, while the power law index n is related to

Table 1
Physico-chemical properties of the polymers used in the work. Data are collected by the manufacturers' notes [21,22].

Polymer	Manufacturer	Degree of substitution (% W/W)		Labelled viscosity[a] (mPa s)
		Methoxy	Hydroxypropyl	
METHOCEL E6	Colorcon	28–30	7–12	6
METHOCEL E15	Colorcon	28–30	7–12	15
METHOCEL E50	Colorcon	28–30	7–12	50
PHARMACOAT 606	Shin-Etsu	28–30	7–12	6
PHARMACOAT 615	Shin-Etsu	28–30	7–12	15
METOLOSE 60SH50	Shin-Etsu	28–30	7–12	50

[a] The viscosity of the polymers is referred to the viscosity of 2% water dispersions at 20 °C.

the flow patterns. Newtonian behaviour is indicated by n values equal to 1, while values lower and higher than 1 suggest shear thinning and thickening behaviour, respectively.

All the polymer solutions systems showed n values very close to 1 (from 0.97 to 1.03, data not shown), indicating that the hypromellose 2910 solutions in the concentration range studied exhibit Newtonian behaviour.

Concerning viscosity, as expected, the results showed strong concentration and molecular weight dependence (Fig. 1), but no significant differences between polymers of the same molecular weight from different manufacturers. In particular, Methocel E6-Pharmacoat 606 and Methocel E15-Pharmacoat 615 were practically superimposable.

In the development and optimisation of a spray coating process, rheological behaviour and viscosity of polymeric solutions represent two key parameters. During coating, the polymeric solutions should possess a sufficiently low viscosity, which means low polymer concentration, in order to assure an optimal spraying process. However, relatively high polymer content guarantees shorter drying phases and higher process efficiency [15]. As these issues are in stark contrast, a compromise must be found in order not to penalise the quality or the efficiency of the coating process. A balance can be struck by using the viscosity range 150–400 mPa s, although higher viscosities may be possible under certain equipment conditions [21]. Given this information, polymer solutions were selected in concentrations that provided a viscosity of about 400 mPa s, deemed fit not only for a real coating process but also for the casting procedure.

3.2. Thermogravimetric analysis of free films

In order to perform an accurate thermo-mechanical analysis of free films, it is necessary to reduce or eliminate any possible source of errors. Since the free films were prepared by casting from aqueous solutions, a key parameter is the film water content. Water acts as a plasticiser, influencing the mechanical parameters and therefore the reliability of tests such as the strain or frequency sweep.

The TGA plots for Methocel free films are reported in Fig. 2. The weight loss curves showed that the water removal begins at 30 °C and carries on up to 125–135 °C. Above 200 °C, a further decrease of the sample weight indicated the beginning of hypromellose degradation. An easier and more powerful way to analyse the TGA output is to use the first derivative dWl/dT. The first derivative
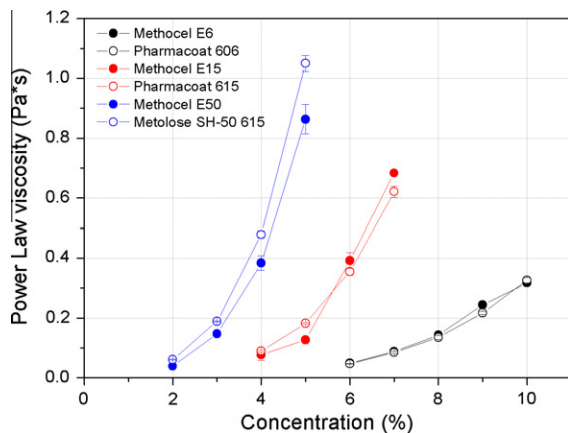

Fig. 2. Thermogravimetric analysis of Methocel free films. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

represents the weight loss rate, so values of 0 indicate no weight variation, while negative values define a weight loss process, and positive values an absorption process. Curves in Fig. 2 clearly pointed out that the water removal continues beyond 100 °C, with the highest rate around 75 °C.

Similar results were also found for Pharamacoat and Metolose free films, which always gave a water content between 6.5 and 7.3% w/w.

3.3. Dynamic mechanical analysis of free films

DMA analysis makes it possible to characterise the mechanical properties of materials through the study of their behaviour as a function of the rate of the applied stimuli (frequency) or the change of the environmental conditions (temperature or moisture). However, before performing any measurement, it is necessary to find out the linear viscoelastic region, that is, the region where the observed viscoelastic properties are independent of the imposed stress or strain. Only in this region the mechanical and viscoelastic properties can be related to the analysed materials independently of any influences from the experimental set up.

As an example, the plot of a strain sweep test is reported in Fig. 3. At low displacement amplitude (lower than 1%), scattered data were observed, while at high displacement amplitude (above 5%), a continuous modulus decrement indicates that strain is outside the LVR. Therefore, the region comprised between 1% and 5%

Fig. 1. Influence of hypromellose viscosity type and concentration on the viscosity of their aqueous solutions. Error bars refer to the standard deviation (for low standard deviations, the bars are hidden by the symbols). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
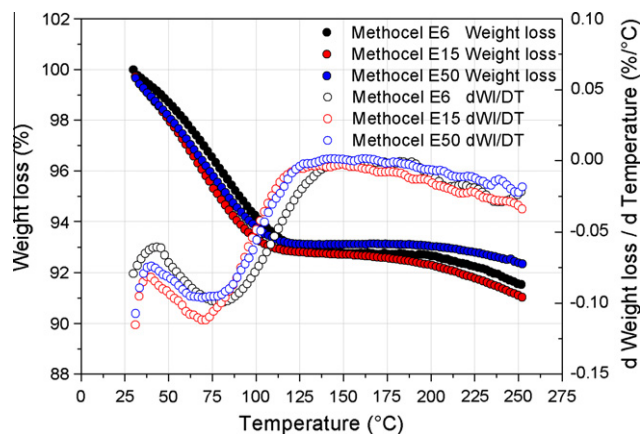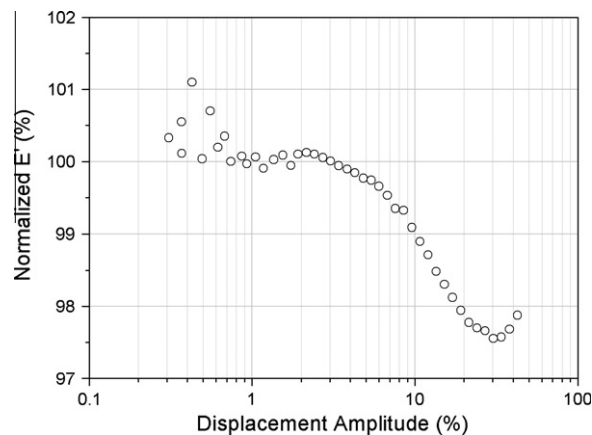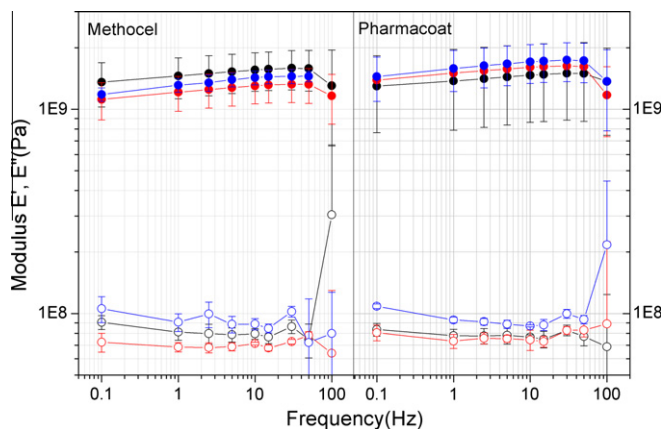

Fig. 3. Strain sweep for a sample of Methocel E6 free film.

of displacement amplitude represents the LVR, where the modulus is independent from the experimental parameters.
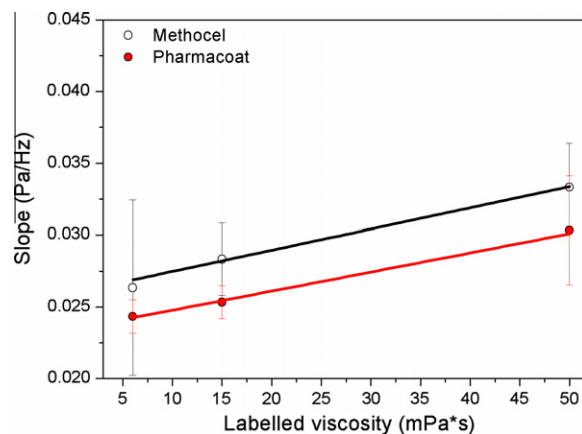
Frequency sweep tests allow comparison of film mechanical properties and study of the material viscoelasticity. The results obtained (Fig. 4) showed no significant difference between the two brands of polymers and among the three viscosity types in term of storage and loss modulus. There is always a strong preponderance of the storage modulus over the loss modulus and also a low dependence on the frequency, suggesting that all the polymers were analysed in the frequency range defined as the glassy region (the absolute values agree with those found by Perfetti et al., on the glassy region of Pharmacoat 606 and 615 [15]). This means that the polymer relaxation time distributions are centred at higher times than those analysed. For an accurate analysis, it would be necessary to extend the frequency range to much lower values, which is possible only by applying the time–temperature superposition. However, this approach is particularly time consuming and affords no real practical improvement, since it should be investigated at very high frequency values, far removed from those to which a film may be subjected during its actual use (the 0.1–100 Hz range already represents a wider frequency range than that to which the material would normally be subjected).

The time-dependent behaviour of the analysed polymers can be empirically evaluated by comparing the slopes of the frequency sweep plots. The results, reported in Fig. 5, showed a linear correlation between the polymer time dependency and the labelled viscosity (that corresponds to the molecular weight), indicating that the molecular relaxation time distributions are slightly different according to the polymer chain length. No differences were found in the time-dependency behaviour between polymers of the two different brands, which showed the same trend.
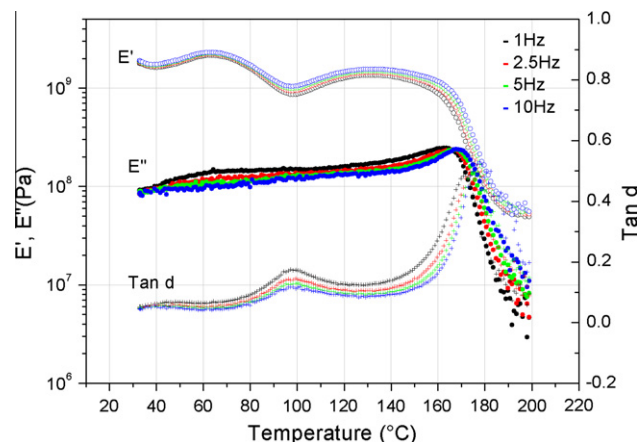
Temperature sweep tests are the most common type of analysis in DMA, often used to characterise temperature-dependent transitions of amorphous materials. A typical temperature sweep test is reported in Fig. 6. As the temperature increases, the E' begins to zdecrease slightly, representing a reduction of the material stiffness, up to a characteristic temperature value (glass transition temperature) where there is a large drop of the modulus, indicating the transition from a glassy to a rubbery state. The transition is also evident as a small peak in the loss modulus or as a high peak in the tan d plot. The obtained curves show a typical trend of amorphous materials as reported by many authors [14,15,24–26]. In addition to the glass transition observed around 170 °C, a smaller peak is evident in the tan d plot around 90 °C. Similar secondary

Fig. 5. Variation of the time-dependency parameter (slope of the E' frequency spectrum) in function of the polymers molecular weight. Error bars refer to the standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 6. Example of a temperature sweep test (data refer to a Methocel E50 sample). The symbol ○, ●, +, refer to E', E'' and tan d respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

peaks were also found in the literature for hypromellose films [27] and tablets [28]. From the shape of the E' plot (the presence of two humps before and after the tan d peak) and the TGA curves, such a transition could be attributed to water evaporation. This hypothesis is also confirmed by the differential scanning calorimetry (DSC) and modulated differential scanning calorimetry (MDSC) data reported by Gómez-Carracedo et al. [28]. In that work, a broad endothermic peak, interpreted by the authors as the evaporation of the moisture content, was found both in the first heating of the heat flow signal (DSC) and in the non-reversing heat flow signal (MDCS) at the temperatures corresponding to the smallest tan d peak in the oscillatory rheological plots.

Glass transition temperatures of the polymers were assumed as the maximum of tan d peak traces determined at a frequency of 1 Hz. The results (Table 2) showed a positive correlation between the Tg values and the polymer labelled viscosity for both the analysed brands. A similar trend was found for hypromellose 2910 films in a previous work [15], even if only two different viscosity types were analysed.

Temperature sweep carried out in multifrequency mode also allows a more detailed analysis of the glass transitions. Since Tg is a relaxation process, it depends on the frequency applied, because the molecules can begin to move when their relaxation times

Fig. 4. Influence of the applied frequency on the mechanical parameters E' and E''. The full circles refer to E' while the empty circles indicate E''. The colours black, red and blue refer to viscosity type 6, 15 and 50 respectively. Error bars refer to the standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Glass transition temperature (Tg), apparent activation energy (Ea) and fragility parameter (m) of the different film prepared.

Film composition	Tg 1 Hz (°C)	Ea (kJ/mol)	m	R^2 of the Arrhenius plot
METHOCEL E6	164.3 ± 1.1	714.1 ± 37.7	84.7 ± 4.3	0996 ± 0002
METHOCEL E15	167.0 ± 0.6	670.8 ± 95.3	79.1 ± 11.2	0995 ± 0004
METHOCEL E50	171.4 ± 0.3	620.8 ± 24.9	72.4 ± 2.9	0993 ± 0008
PHARMACOAT 606	161.4 ± 1.5	673.7 ± 54.9	80.4 ± 6.3	0996 ± 0004
PHARMACOAT 615	164.9 ± 1.1	627.5 ± 44.1	74.2 ± 5.0	0993 ± 0001
METOLOSE 60SH50	171.1 ± 0.4	573.1 ± 33.7	66.9 ± 3.9	0996 ± 0002

approach the frequency of the oscillating strain [20,29]. The frequency dependence of the glass transition temperatures can be used to calculate the apparent activation energy (Ea) of the transition using a simil-Arrhenius equation [20,29,30]:

$$\ln f = \ln A - \frac{Ea}{RT} \qquad (2)$$

where f is the frequency, A is a constant, R is the gas constant and T is the glass transition temperature (in K) at the frequency f. The activation energy was calculated from the slope of the natural logarithm of the frequency versus the inverse of the glass transition temperature plot. All the samples showed an Arrhenius behaviour as indicated by the R^2 values in Table 2, with activation energy values between 570 and 715 kJ/mol. The Arrhenius behaviour of hypromellose and the activation energy value (around 700 kJ/mol) were previously reported [19], even if only for a viscosity type in powdered form. Data reported in Table 2 showed a negative correlation between the activation energies and the polymer viscosity grade for the products from the two different manufacturers, without any significant differences between materials of the same viscosity grade, even if the Colorcon products always presented slightly higher values. Since the Ea represents an apparent stability and molecular mobility parameter for structurally correlated glassy materials [20,30], the data obtained indicated that the glassy hypromellose films possessed an apparent stability proportional to their molecular weight.

From the apparent activation energy values of the glass transition, the fragility parameter (m) can be calculated using the following relationship [26,31,32]:

$$m = \frac{Ea}{2.303RTg} \qquad (3)$$

The fragility parameter, also called 'steepness index', represents the slope of a Tg-scaled Arrhenius plot of any relaxation time (or any other properties related to relaxation time) measured at Tg [26]. This parameter was introduced [33] to differentiate materials according to the variation of their properties through the glass transition. The fragility values make it possible to classify amorphous materials in 'strong and fragile systems'. A strong system ($16 < m < 100$) does not markedly change its properties moving from a glassy to a rubbery phase, while a system is defined fragile ($m > 100$) when its properties vary significantly during the passage through the glass transition [26,32,34].

According to the results reported in Table 2, all the analysed films possessed an m value below 100, so they can be defined as strong systems according to the Angel classification. In this case as well, there is a clear relationship between the m parameter and the polymer viscosity grade, indicating that the material fragility decreases as the chain length increases. From these results, it is evident that the fragility parameter is inversely correlated with the apparent activation energy. It seems that for chemically correlated compounds, the higher the glassy phase stability, the higher the change of polymer properties through the glass transition. A similar correlation can be found in different amorphous polysaccharides using

DSC analysis [35] and also for polymers with different water content analysed by DMTA [26,34,36].

Comparison of the Tg and associated parameters of the products of the two manufacturers did not show sharp differences between polymers of the same labelled viscosity, even if Shin-Etsu products always showed slightly lower values of all the measured parameters.

4. Conclusion

In this paper, a dynamic mechanical thermal analysis of hypromellose 2910 films was performed taking into account the influence of polymer molecular weights (corresponding to viscosity grade) and brands.

At room temperature, the mechanical properties of the free films were independent of the molecular weight or the manufacturer, even if the mechanical properties of high molecular weight polymers appeared slightly more sensitive to the rate of the applied stimuli. The different polymer grades analysed showed different properties during the heating process. Glass transition temperature, apparent activation energy and fragility depended on the polymer chain length; in particular, low molecular weight materials showed higher stability of the glassy phase but also higher fragility moving through the glass transition. Polymers of the same molecular weight but different manufacturer showed the same trends even if the absolute values were slightly different.

In conclusion, the mechanical properties of hypromellose 2910 free films in the glassy phase are practically independent of the grade and the manufacturer, though polymer molecular weight represents an important factor for the transition from a glassy to a rubbery phase.

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