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# Glassy state molecular mobility and its relationship to the physico-mechanical properties of plasticized hydroxypropyl methylcellulose (HPMC) films



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## ABSTRACT

Changes in tensile properties and the glass transition temperature ( $T_g$ ) of plasticized polymer films are typically attributed to molecular mobility, often with no empirical data to support such an assertion. Herein solvent cast HPMC films containing varying amounts of PEG, as the plasticizer, were used to assess the dependence of tensile properties and the  $T_g$  on glassy state molecular mobility. Molecular mobility (molecular relaxation time and temperature) parameters were determined by Thermally Stimulated Current Spectroscopy (TSC). The tensile properties and  $T_g$  of the HPMC films were determined by texture analysis and DSC, respectively. Molecular mobilities detected by TSC were cooperative and occurred at temperatures ( $T_g'$ ) well below (113 to 127 °C) the bulk  $T_g$ . The relaxation times ( $\tau$ ) were  $71 \pm 1$ ,  $46 \pm 1$ ,  $42 \pm 1$ ,  $36 \pm 1$  and  $29 \pm 1$  s for HPMC films containing 0, 6, 8, 11 and 17% (w/w) PEG, respectively. The  $T_g$  and glassy state molecular mobility were found to be intimately linked and demonstrated a linear dependence. While tensile strength was found to be linearly related to molecular relaxation time, tensile elongation and elastic modulus exhibited a non-linear dependence on molecular mobility. The data presented in this work demonstrates the complex nature of the relationship between plasticizer content, molecular mobility,  $T_g$  and tensile properties for plasticized polymeric films. It highlights the fact that the dependence of the bulk physico-mechanical properties on glassy state molecular mobility, differ greatly. Therefore, empirical characterization of molecular mobility is important to fully understand and predict the thermo-mechanical behavior of plasticized polymer films. This work demonstrates the unique capability of TSC to provide key information relating to molecular mobility and its influence on the bulk properties of materials. Data generated using TSC could prove useful for stability and performance ranking, in addition to the ability to predict materials behavior using data generated at or below typical storage conditions in the pharmaceutical, food, and polymer industries.

## 1. Introduction

Hydroxypropylmethyl cellulose (HPMC), also known as hypromellose, is a cellulose based synthetic polymer that is considered safe for human consumption, and has broad application in the food and pharmaceutical industries (Burdock, 2007; Shit and Shah, 2014). As an excipient, HPMC functions as a thickener, binder, bio-adhesive or solubility enhancer (Jaya et al., 2012; Chowdary et al., 2014; Huichao et al., 2014). HPMC also possesses good film forming properties and is a common excipient in pharmaceutical film formulations including film coated tablets (Missaghi and Fassihi, 2006; Al-Tabakha, 2010; Karki et al., 2016). The use of HPMC as an alternative to gelatin in capsule formulations has been of interest, as it offers distinct advantages. For

example, it is of a vegetable source and therefore by-passes the stringent regulations imposed on the use of materials of animal origin in pharmaceutical products by regulators (Ku et al., 2011). This advantage over gelatin has been a key driver for the development of HPMC based capsules i.e. Vegicaps Soft (Catalent Pharma Solutions) and hard capsules such as Vcaps Plus (Capsugel) (Missaghi and Fassihi, 2006; Ku et al., 2011).

An important characteristic of any capsule or film-based product is their ability to withstand mechanical damage and exhibit the appropriate level of flexibility (Al-Tabakha, 2010; Curtis-Fisk et al., 2012) to enable easy handling and processing. The characterization of mechanical properties and the ability to predict the influence of formulation parameters on these properties is therefore important in the

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development of polymer films for pharmaceutical applications.

The mechanical properties of films are typically described by tensile strength, elongation and elastic (Young's) modulus. These properties are commonly measured by means of uni-axial tensile stress testing, on a section of isolated film. It is well established that the measured mechanical properties of a piece of film are influenced by temperature and plasticizer concentration. For example, polymers exhibit stiff/brittle behavior at temperatures below the glass transition temperature ( $T_g$ ), while at temperatures above the  $T_g$ , they are flexible/ductile materials (Smith et al., 2009; Karki et al., 2016) and may even flow. Plasticizers are key components for optimizing mechanical properties in film formulations. Increasing the amount of plasticizer enhances flexibility, workability or distensibility by reducing the melt viscosity. This is typically associated with a decrease in the  $T_g$  and elastic modulus values (Honary and Orafi, 2002; Daniels, 2009). In addition, the molecular weight of plasticizers has also been shown to be a factor in plasticizer efficiency (Honary and Orafi, 2002).

Several theories exist to explain the mechanism by which plasticizers change the thermal and mechanical properties of polymeric films. The most widely known are the lubricity, gel and free volume theories (Daniels, 2009; Marcilla and Beltran, 2017). While details of these theories are beyond the scope of this article, it is important to note that each theory implies that the degree of motional freedom in plasticized materials is the most essential property governing thermo-mechanical behavior.

Various analytical techniques have been employed to investigate molecular mobilities in polymer films. Techniques such as de-wetting (Connie and John, 2005; Wang and McKenna, 2013), ellipsometry (Tress et al., 2010; Inoue et al., 2009; Mok et al., 2010), neutron scattering (Inoue et al., 2009; Soles et al., 2002; Soles et al., 2003; Clough et al., 2011), fluorescence spectroscopy (Connie and John, 2005; Roth et al., 2007; Priestley et al., 2007; Kim et al., 2008), X-ray reflectivity (Wallace et al., 1995; Weber et al., 2001), Brillouin light scattering (Forrest et al., 1997; Mattsson et al., 2000; Fukao et al., 2001), secondary ion mass spectroscopy (Zheng et al., 1997; Pu et al., 2001; Connie and John, 2005) and dielectric spectroscopy (Priestley et al., 2007; Yin et al., 2012; Yin et al., 2013; Tress et al., 2010; Serghei et al., 2005) have all been used to interrogate the molecular mobility characteristics of polymer films. These studies have often been focused on motional dynamics at varying thickness of polymer films on a solid support or free-standing. Collectively, these studies provide a wealth of information on molecular mobility at small thickness scales. Whilst this is important and provides interesting information on the mobility of confined polymers for several fields of application e.g., microelectronic, optoelectronics and biological sensors (Pique et al., 2003; Hojati-Talemi et al., 2013), they do not address the relationship between molecular mobility and the bulk properties of polymer films for pharmaceutical applications. Furthermore, empirical studies in the literature investigating the direct relationship between parameters of glassy state molecular mobility, and thermo-mechanical properties of polymer films are scarce, and therefore require investigation.

In this work Thermally Stimulated Current (TSC), a relatively simple dielectric analysis technique, was employed to characterize molecular mobility in the glassy amorphous state of plasticized HPMC films. An attempt is made to relate the parameters of molecular mobility (ease and rate of mobility) to the tensile properties of the plasticized films and the  $T_g$ .

Details of the TSC technique can be found elsewhere (Turnhout, 1975; Ramos and Mano, 1997; Correia et al., 2000; Owusu-Ware et al., 2013). Briefly, TSC measures currents generated by the movement of molecular dipoles, as a function of temperature, in response to externally applied static electrical field. The external electrical field polarizes molecules in the material i.e. causing bonds, atoms and whole/segments of molecules to align against an externally applied electrical field. This polarization is "frozen-in" by quench cooling to a temperature well below the temperature of polarization, at which point the

external electrical field is removed. During heating, the "frozen-in" polarizations relax (depolarize) i.e. molecules, parts of molecules, and dipoles move back to their native orientations, generating measurable currents. The shape, size and temperature of the current signal is dependent on the type of relaxation, the rate and the ease with which the different activated relaxations occur, in addition to the fraction of molecules undergoing relaxation. This makes it possible to characterize the distinct types of molecular dipole relaxations (molecular mobilities) in polymer films i.e.,  $\alpha$ -relaxation that is associated with the glass transition and the more subtle secondary relaxations ( $\beta$  and  $\gamma$  type relaxations). Since the current generated is proportional to the externally applied electrical field, the sensitivity of the instrument can be controlled by the operator. Furthermore, TSC is known to have better resolution and sensitivity to the different modes/types of molecular relaxation when compared with dielectric spectroscopy analysis (DEA) and dynamic mechanical analysis (DMA) (Saffell et al., 1991; Grein et al., 2004; Ramos et al., 2004; Barker and Antonijevic, 2011).

There are two main experiments that can be performed using TSC, namely Thermally Stimulated Depolarization Current (TSDC) and Thermal Windowing (TW) (Turnhout, 1975). In TSDC experiments the sample is simply polarized at a defined temperature (the polarization temperature ( $T_p$ )) for a time (polarization time ( $t_p$ )) long enough to obtain equilibrium saturation of the various molecular orientations in the material. This is then 'frozen in' by cooling to a temperature ( $T_0$ ) well below the  $T_p$  before a linear heating ( $\beta$ ) is applied from  $T_0$  to a final temperature ( $T_f$ ) that is higher than the  $T_p$ .

The second experiment, the TW, is used to deconvolute the complex TSDC signal into its various discrete relaxation modes (those that have different relaxation times and activation energies). Here, a narrow temperature window of polarization ( $T_w$ ) is applied covering the entire width of the global TSDC signal. Each polarization is followed with a depolarization step, whereby the relaxation modes with the fastest relaxation time are removed from the system by cooling the sample to a few degrees below the initial polarization temperature ( $T_d$ ). At this point, the external electrical field is short circuited as the sample is held isothermal for a brief time ( $t_w$ ). The remaining slower relaxations are 'frozen in' on cooling and relax back to their native orientation upon heating. The discrete relaxation processes detected are used to generate a map of relaxation times and enthalpy of activation by means of the Eyring kinetic model fitting, which are then used to determine the types of relaxations exhibited by the material under investigation.

## 2. Experimental

### 2.1. Materials

Hydroxypropyl methylcellulose (HPMC) (average molecular weight ~860 kDa, viscosity of 1% (w/v) aqueous solution at 20 °C of ~145 mPa.s) and PEG 400 were purchased from Sigma Aldrich (Gillingham, UK).

### 2.2. Methods

#### 2.2.1. Preparation of films

Films were prepared using the solvent casting method. Aqueous gels (2% w/w) consisting of 0, 6, 8, 11 and 17% w/w PEG 400 were prepared in deionized water (heated to 60 °C) and the mixture stirred at ambient temperature overnight (~18 h in total). 50 g of the gel was poured into a plastic Petri dish (diameter of 140 mm) and left in a 60 °C oven for 24 h. The resultant films were stored in a desiccator over silica for two days before analysis. The films that were optically clear with no visible defects were chosen for analysis. The thickness of the films was determined using a digital caliper and found to be  $0.047 \pm 0.001$  mm. XRPD analysis was performed and showed the films to be completely amorphous.

### 2.2.2. Thermogravimetric analysis (TGA)

TGA studies were performed using a Q5000 IR (TA Instruments, UK). A sample mass of  $3.2 \pm 0.5$  mg was used for all compounds. Samples were subjected to heat-cool-heat experiments under a nitrogen atmosphere at a flow rate of 25 mL/min in hermetically sealed Tzero aluminium pans with a single pin hole in the lid. Each sample was heated from ambient temperature to 150 °C at a heating rate of 10 °C/min, cooled back to 25 °C and reheated to 150 °C at 10 °C/min.

### 2.2.3. Differential scanning calorimetry (DSC)

DSC studies were performed using a Q2000 calorimeter (TA Instruments, UK) under a nitrogen atmosphere at a flow rate of 50 mL/min, using hermetically sealed Tzero aluminium pans with a pin hole in the lid. Sample masses of  $2.60 \pm 0.24$  mg were heated to 140 °C to remove moisture, equilibrated at  $-90$  °C, held isothermally for 5 min and heated to 200 °C at 10 °C/min.

### 2.2.4. Texture analysis

The mechanical (tensile) properties of the HPMC films were analyzed at ambient temperature with a TA HD plus (Stable Micro System, UK) texture analyzer. The films ( $n = 3$ ) devoid of any visible physical defects were cut into dumb-bell shapes. A trigger force of 0.1 N was applied during the testing and the films stretched between two tensile grips at a speed of 0.2 mm/s to a maximum distance of 300 mm or until the films broke. The % elongation at break, the tensile strength and elastic modulus were determined (Lim and Hoag, 2013).

### 2.2.5. Thermally stimulated current (TSC) experiments

TSC studies using the thermally stimulated depolarization current (TSDC) experiment, covering the range  $-100$  to 70 °C were conducted with a TSCII/RMA spectrometer (SETARAM, France) equipped with a 900 series LN2 (Liquid Nitrogen) micro-dosing cooling system (Norhof, Netherlands) and 6517A electrometer (Keithley, USA). Experiments were performed using electrode arrangement that consists of bottom (13 mm diameter) and upper (10 mm diameter) steel electrodes. The sample diameter of the film cut for analysis was  $12.0 \pm 0.5$  mm and the surface area of the sample in direct contact between the top and the bottom electrode was 78.54 mm<sup>2</sup>. The analysis chamber was evacuated to  $10^{-4}$  mbar and flushed several times with high purity helium (1.1 bar) prior to analysis. Each sample was initially subjected to a pre-treatment in which it was heated to 60 °C (the film forming temperature) and held isothermal for 30 min. This was followed by evacuation of the analysis chamber to  $10^{-4}$  bar and flushing three times with high purity helium (1.1 bars). The global TSDC signals were obtained by polarizing the sample at 60, 5,  $-5$ ,  $-12$ , and  $-30$  °C for films containing 0, 6, 8, 11, and 17% w/w PEG 400, respectively, using polarization field ( $E_p$ ) ranging from 50 to 250 V/mm in increments of 50 V/mm for 2 min ( $t_p$ ). In the case of thermal windowing experiments (TW), samples were polarized with  $E_p = 250$  V/mm at  $T_p$  at 2 to 65 °C,  $-60$  to 33 °C,  $-60$  to 39 °C,  $-60$  to 9 °C and  $-72$  to  $-12$  °C for films containing 0, 6, 8, 11 and 17% PEG 400, respectively, in increments of 3 °C. The temperature range chosen ensured that the thermal windowing experiments covered the whole temperature range of the global TSDC signal.  $T_w$  was set at 3 °C, whilst  $t_p$  and  $t_w$  were set at 2 min for all four samples.

## 3. Results and discussion

### 3.1. TGA and DSC

All samples analyzed (HPMC and HPMC with different percentage of PEG) were found to lose 4–6% moisture when heated from ambient temperature to 150 °C and this dehydration process occurred below 120 °C, which was the removal of free water. As shown in Fig. 1, the second heating profile was practically flat, indicating complete removal of water from the films when heated to 150 °C.

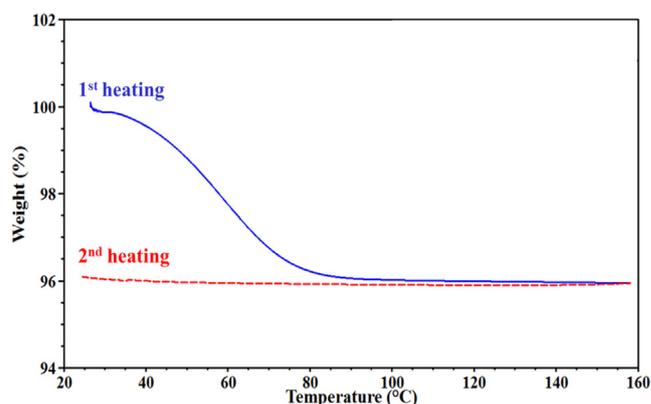


Fig. 1. A typical overlay of TGA thermograms obtained for the first and second heating of HPMC films with varying PEG contents.

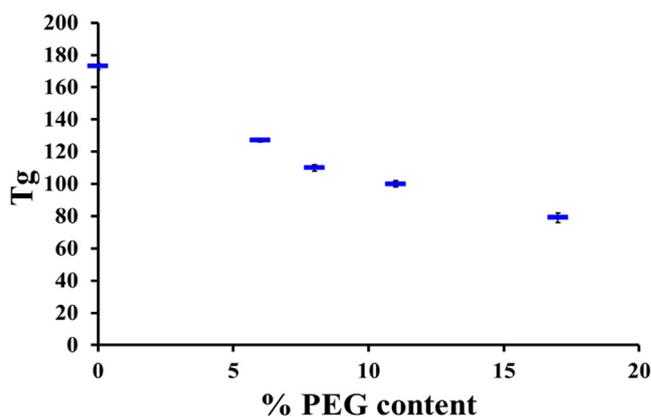


Fig. 2. A plot showing the relationship between  $T_g$  and PEG content (% w/w) of the HPMC-PEG films.

The DSC data presented in Fig. 2 showed that the bulk  $T_g$  of the films decreased with increasing PEG content, which is typical behavior of polymeric films (Khodaverdi et al., 2012). The decrease in  $T_g$  as a function of PEG content in the HPMC films is non-linear i.e. a sharper decrease in  $T_g$  was observed from 0 to 8% PEG, beyond this point the magnitude of the change in  $T_g$  as a function of PEG decreases, with the plot moving towards a plateau. This demonstrates that beyond a certain PEG content (% w/w) the efficiency of plasticization decreases and therefore greater amount of PEG is required to cause further decrease in the  $T_g$ .

One of the most important influences of plasticizers on the glass transition process observed in DSC, and often disregarded, is the decrease in the steepness and increase in the width of the glass transition process. This occurs because plasticizers reduce the energy difference between the glassy and rubbery phase by facilitating an increased degree of molecular mobility i.e., molecules of plasticized films in the glassy state exhibit an increasingly higher state of mobility and therefore kinetic energy, with increasing plasticizer content. This presents a problem in detecting the  $T_g$  of plasticized films, as the energy change associated with the glass transition process becomes too small to detect by DSC. Khodaverdi and colleagues (2012) highlighted this problem in their investigation comparing different plasticizers and their effect on the thermo-responsive properties of Eudragit RS films. In their work  $T_g$  data could not be provided for the Eudragit RS film plasticized with 20% triethyl citrate (TEC) plasticizer, because it could not be detected by DSC. This impacts on the ability to make a direct comparison between two or more plasticizers with different plasticization efficiency across a broad range of concentrations/% content. In these situations TSC is, perhaps, one of the most useful technique to use to overcome such issues (Antonijevic et al., 2008).

**Table 1**

Summary of the tensile strength, percent elongation at break and elastic modulus of HPMC films with increasing PEG 400 (% w/w) content.

% PEG content (w/w)	Tensile strength (MPa)	% Elongation at break	Elastic modulus (MPa)
0	31 ± 2	4 ± 1	1271 ± 105
6	26 ± 2	8 ± 2	1050 ± 147
8	25 ± 2	9 ± 3	971 ± 117
11	23 ± 1	11 ± 3	903 ± 104
17	21 ± 2	23 ± 1	565 ± 54

### 3.2. Texture analysis

The data obtained from the texture analysis are presented in Table 1. The results obtained were consistent with what is generally expected for a plasticized polymeric film. Increasing plasticizer concentration increased elongation at break, whilst the tensile strength and elastic modulus decreased.

Elongation is the extendibility of the film from the initial length to the point of break and it quantifies the flexibility/ stretchability of films. The increase in elongation observed as a function of plasticizer concentration, can be explained by the reduction in inter-molecular attractive forces between HPMC molecules (Lim and Hoag, 2013). This disruption of the strong interactions between HPMC molecules by the PEG molecules reduces rigidity and increases the flexibility of the film by promoting HPMC polymer chain mobility. Replacement of strong intermolecular interactions between HPMC molecules by weaker HPMC-PEG interactions also explains the decrease in the tensile strength observed as PEG concentration is increased. Elastic modulus measures the resistance of the film to elastic deformation, and provides information on the film stiffness/strength (Lim and Hoag, 2013). This was also found to decrease, as expected, with increasing plasticizer concentration.

### 3.3. Thermally stimulated depolarization current (TSDC)

For this study only the initial global TSDC peak detected for each sample was considered. There were two main reasons for excluding signals beyond the initial global TSDC peak; firstly, it was found that the current signal generated after the initial relaxation process (first peak) appears to increase infinitely in each sample (examples provided in section B of the Supplementary Information). In these situations, it was not possible to decipher contributions from molecular dipole relaxations and movement of other charged species. Secondly the first peak had a similar shape and was consistent across all samples. It was therefore considered to originate from the same type of relaxations, which enabled direct comparison between the samples analyzed.

The current signal generated from TSDC experiments can arise from the movement of various charged species, originating from several polarization mechanisms i.e. electronic, atomic, space charge, interfacial and molecular dipole polarization (Ibar, 1993; Turnhout, 1975). When investigating parameters associated with molecular mobility, it is important to ascertain that the TSDC output is due to molecular dipole relaxations. In order to determine this, samples were analyzed several times with increasing electrical field strengths. In the case of a molecular dipole relaxation, a linear relationship should exist between the ratios of the applied electrical field strength and the total polarization (P) (area under the TSDC signal) (Correia et al., 2000; Diogo et al., 2008; Pinto et al., 2010).

The TSDC signals obtained for the samples analyzed proved to originate from molecular dipole relaxations i.e. linear regression of the ratio of applied electrical field strength against the ratio of the polarization generated, yielded  $r^2$  values > 0.994 and a slope close to unity (> 0.91 < 1.1), for all samples analyzed. Hence the TSDC profile obtained in this study represent the relaxation/mobility of polarized

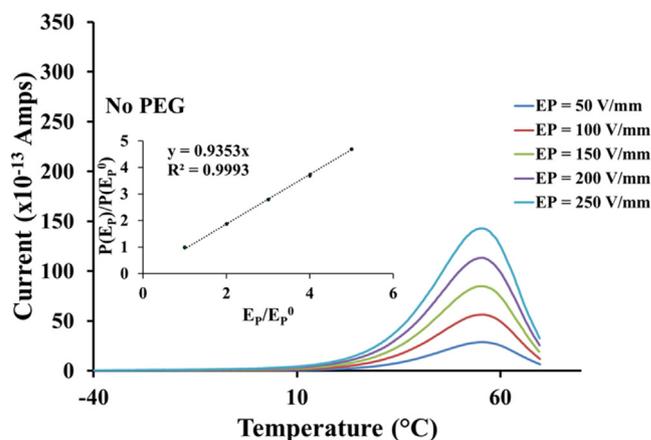


Fig. 3. TSDC signals obtained with increasing electrical field strength ( $E_p$ ) for HPMC films in the absence of PEG. The insert shows the linear relationship between the ratios of electrical field strength and polarisation (P) for the HPMC films (no PEG).

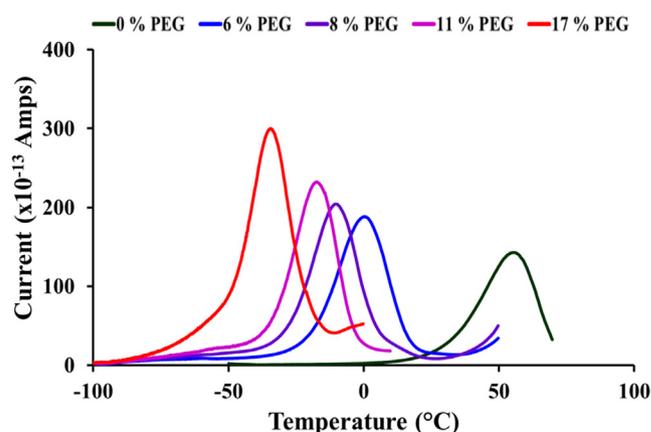


Fig. 4. TSDC molecular relaxation signals obtained using an electrical field strength ( $E_p$ ) of 250 V/mm for HPMC films containing 0, 6, 8, 11 and 17% (w/w) PEG 400.

HPMC and PEG molecules. Fig. 3 shows a typical output of these TSDC experiments. Increasing PEG concentration (% w/w) was found to decrease the temperature of molecular dipole relaxation (Fig. 4). The relaxation peak temperature ( $T_m$ ) of the un-plasticized HPMC film was detected at  $56.0 \pm 0.7^\circ\text{C}$ , whilst films containing 6, 8, 11 and 17% (w/w) PEG were observed at  $-0.3 \pm 0.8^\circ\text{C}$ ,  $-9.0 \pm 1.1^\circ\text{C}$ ,  $-18.6 \pm 1.4^\circ\text{C}$  and  $-33.8 \pm 1.0^\circ\text{C}$ , respectively. The results also showed increased intensity/size of relaxation current generated with increasing PEG content. These findings showed that the addition of PEG to HPMC films both enhanced the amount/extent of molecular mobility and the ease with which mobility occurred in the glassy state.

A plot of PEG content and the  $T_m$  was found to follow a similar profile to that observed between PEG content and the  $T_g$  determined by DSC (Fig. 5) i.e., an initial, relatively sharp decrease in  $T_m$  with increase in PEG content up to 8%, from which point the change in  $T_m$  as a function of PEG content decreases, tending towards a plateau. This demonstrates that molecular mobility, well below the glass transition process, and the  $T_g$  itself are influenced in a similar way by PEG and supports the idea that glassy state molecular mobility and the bulk glass transition process are intimately linked.

### 3.4. Thermal windowing (TW) results

The application of the thermal windowing experiments deconvoluted the complex global relaxation peak into discrete relaxation

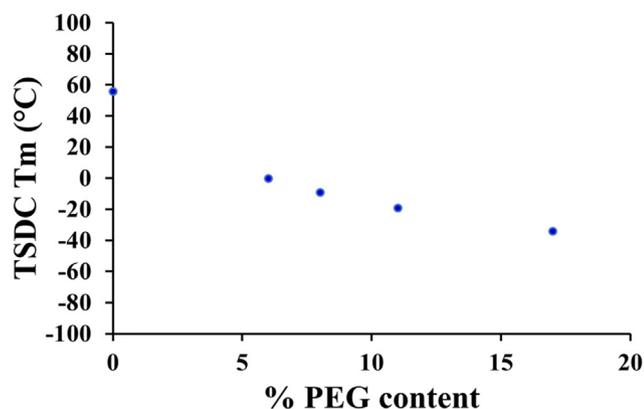


Fig. 5. A plot showing the relationship between TSDC T<sub>m</sub> and PEG content (% w/w) of the HPMC-PEG films.

processes. As shown in Fig. 6, all the PEG plasticized HPMC films exhibit two groups of discrete relaxation processes within the temperature range of the analysis. The first group (lower temperature grouping) corresponds to the global relaxation process identified in the TSDC investigations. The second group of relaxations are part of the infinitely increasing TSDC signal (section B of the Supplementary Information). It was not possible to assess the existence of this second group of

relaxations for the HPMC films in the absence of PEG as heating these samples above 70 °C was suspected to cause a change to the nature of the material (and hence mobility) in subsequent experiments. Both groups of discrete relaxation processes, only identified in the HPMC films containing PEG, increased with increasing PEG content. However, the relative intensity of the second group of discrete relaxation processes (relative to the first group of discrete relaxation processes) appeared to increase more in step with the increase in PEG concentration. This implied that this group of relaxations mostly originated from the movement of PEG molecules, and were assigned to the increased number of mobile dipoles in PEG molecules compared to HPMC molecules. The current signals associated with these processes were very noisy and inconsistent, due to contributions from space and interfacial charges. As a result, they do not form part of the discussion relating to this work.

The inserts in Fig. 6 show the distribution of relaxation times ( $\tau$ ), referred to as the Bucci lines, for each discrete relaxation process. Straight Bucci lines generally indicate narrowly distributed activation energies, and imply a single mode of molecular relaxation e.g., twisting of polymer end group or orientation of a single fragment of the polymer chain. Bucci line curvature, on the other hand, suggests activation energies are not narrowly distributed, therefore each 'discrete' relaxation process may in fact contain two or more different modes of molecular orientations (Alvarez et al., 2000; Correia et al., 2000; Diogo and Ramos, 2008; Viciosa et al., 2010). This suggests activation of two or

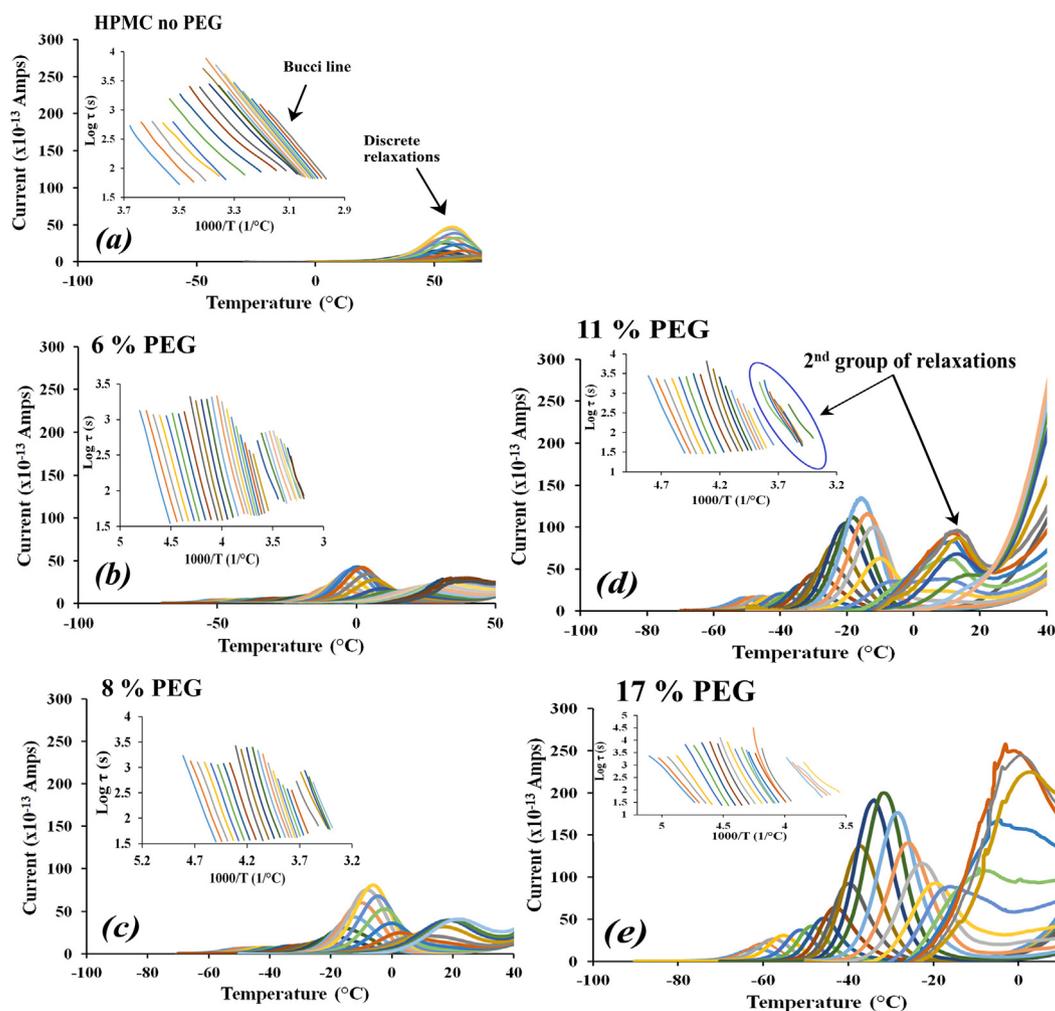


Fig. 6. TW output showing the discrete relaxation processes obtained for (a) un-plasticised HPMC films and HPMC films containing (b) 6%, (c) 8%, (d) 11% and (e) 17% (w/w) PEG 400. The inserts display the Bucci lines obtained for each discrete relaxation process.

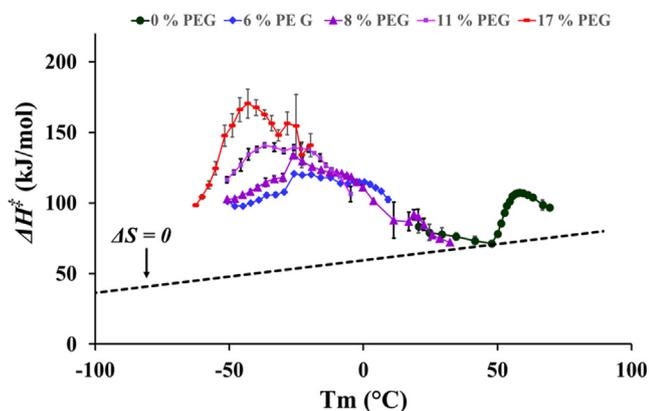


Fig. 7. Overlay of the plots of the enthalpy of activation ( $\Delta H^\ddagger$ ) values for the discrete relaxation process and the zero-entropy prediction ( $\Delta S^\ddagger = 0$ ) obtained for un-plasticized HPMC films and HPMC films containing 6%, 8%, 11% and 17% (w/w) PEG 400.

more groups of molecular fragments with different activation energies. In this study the Bucci lines obtained for the first group of relaxation processes, were generally found to be straight. Each Bucci line was fitted with the Eyring equation to determine the enthalpy of activation ( $\Delta H^\ddagger$ ), entropy of activation ( $\Delta S^\ddagger$ ) and Gibbs free energy of activation ( $\Delta G^\ddagger$ ). Further details of the determination of these parameters together with the relaxation time ( $\tau$ ) are provided in section A of the [Supplementary Information](#).

The cooperativity of these isolated relaxation processes was investigated by overlaying the enthalpy of activation ( $\Delta H^\ddagger$ ) with zero-entropy predictions in a Starkweather type analysis (Ramos and Mano, 1997), as shown in Fig. 7. In this analysis the assumption is made that  $\Delta H^\ddagger$  values have no entropic contribution ( $\Delta S^\ddagger = 0$ ) when the relaxation process is non-cooperative. For cooperative relaxation processes, the  $\Delta H^\ddagger$  value is assumed to have an entropic contribution ( $\Delta S^\ddagger \neq 0$ ) and will therefore deviate from the zero-entropy prediction line.

The Starkweather analysis provides a means to differentiate between non-cooperative secondary relaxations ( $\beta$ - and  $\gamma$ -relaxations) and the cooperative primary relaxations ( $\alpha$ -relaxation). The un-plasticized HPMC films and the PEG plasticized HPMC films were found to deviate from the zero-entropy predictions, which implies that the molecular relaxation processes identified in each film corresponded to a cooperative relaxation process (cooperative molecular mobility).

It is expected that for cooperative mobility to occur in these films, the backbone of the HPMC polymer molecule would have to move, which would require the cooperative movement/orientation of neighboring HPMC and PEG molecules, causing a cascade of molecular orientations throughout the material. This would typically be associated with a high enough energy that is detectable in DSC experiments. This level of cooperativity was observed at higher temperatures ( $> 70^\circ\text{C}$ ) for these materials by DSC. The fact that the cooperative relaxations in the TSC studies were not detected in the DSC suggests that they were to low in energy and may originate from small groups of HPMC polymer segments in localized regions of the film (Owusu-Ware et al., 2016). That is, small groups of polymer segments that do not cause significant viscous/heat changes in the bulk material to generate a sufficiently large signal to be detected by DSC. These low energy cooperative relaxations are likely to arise mostly from the orientation of the hydroxypropyl methyl side-chains and small units of the HPMC end groups, facilitated by the cooperative orientation of PEG molecules. The TSDC peak temperature ( $T_m$ ) of these cooperative molecular relaxations is denoted  $T_g'$  from here on.

Cooperative molecular relaxations or  $\alpha$ -relaxations, are typically associated with the bulk glass transition and expected to be present at or near the  $T_g$  (Ramos and Mano, 1997; Ramos et al., 2004; Smith and Bedrov, 2007; Diogo and Ramos, 2008; Pinto et al., 2010). Data

Table 2

Data for the cooperative relaxation TSDC peak temperature ( $T_g'$ ), relaxation time ( $\tau$ ), for the highest intensity TW output, and bulk glass transition temperature ( $T_g$ ) obtained for the HPMC films.

% PEG content (w/w)	$T_g'$ ( $^\circ\text{C}$ )	$T_g$ ( $^\circ\text{C}$ )	$\tau$ (s)
0	$56 \pm 1$	$173 \pm 2$	$71 \pm 1$
6	$0 \pm 1$	$127 \pm 1$	$46 \pm 1$
8	$-9 \pm 1$	$110 \pm 2$	$42 \pm 1$
11	$-19 \pm 1$	$100 \pm 2$	$36 \pm 1$
17	$-34 \pm 1$	$79 \pm 3$	$29 \pm 1$

presented in this study demonstrates that this is not the case for all materials. For the HPMC films analyzed, cooperative mobility occurs well below the  $T_g$  (between 113 and 127  $^\circ\text{C}$  below the  $T_g$ ) where localized, low energy molecular relaxations occur. Such information is pertinent for understanding stability implications of plasticized drug loaded polymeric films, where the mobility could result in polymer-drug phase separation and/or crystallization of amorphous drug dispersions. Furthermore, understanding molecular mobility in materials at temperatures below or close to their storage conditions can allow for a better prediction of stability and performance ranking, in addition to offering the opportunity to optimize material performance at the molecular level.

### 3.5. Relationships between molecular mobility, $T_g$ and mechanical properties

The molecular relaxation time ( $\tau$ ),  $T_g'$  and the  $T_g$  for the samples analyzed are presented in Table 2. The relaxation time determined in this study is a measure of the time scale of the cooperative molecular relaxations associated with the  $T_g'$ , and is therefore a direct measure of molecular mobility in the glassy state. The fact that both  $T_g'$  and  $\tau$  decreased with increasing PEG content, demonstrates that PEG enhances the ease and rate of molecular mobility in the HPMC films.

The influence of plasticizers on  $T_g$  and tensile properties is typically linked to molecular mobility, usually with no empirical evidence. As such, the nature of the relationship between mobility,  $T_g$  and tensile parameters is not always clear. Data generated from TSC in this study have identified several important trends between molecular mobility and physico-mechanical properties. For example,  $\tau$  and  $T_g'$  were found to be linearly related to  $T_g$  (Fig. 8). The lower the  $\tau$  or  $T_g'$  the lower the  $T_g$ , and vice versa. This shows that mobility at low temperature regions of the glassy amorphous films (TSC data), are directly related to the glass transition process observed at a much higher temperature in DSC.

The tensile strength of the plasticized HPMC films was also found to be linearly related to  $\tau$  i.e., tensile strength increases as  $\tau$  increases

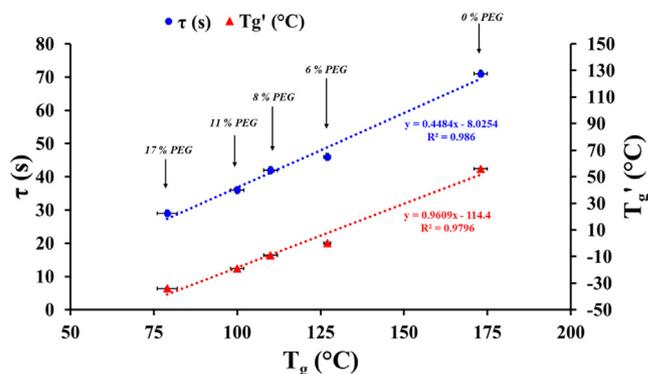


Fig. 8. The relationship between the bulk glass transition temperature ( $T_g$ ), the cooperative relaxation peak temperatures ( $T_g'$ ) and molecular relaxation times associated with the  $T_g'$  for HPMC polymer films containing 0, 6, 8, 11 and 17% (w/w) PEG.

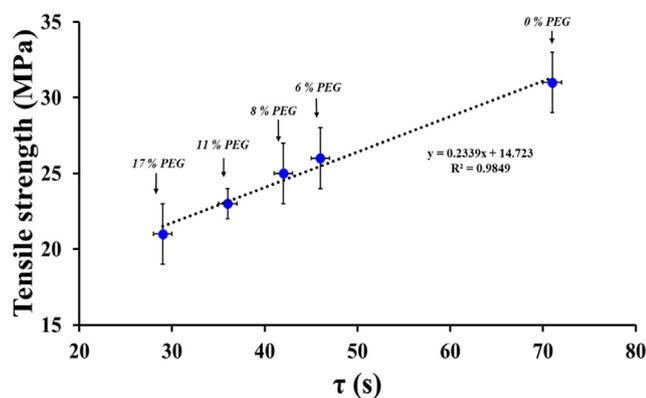


Fig. 9. A plot of the relationship between tensile strength and molecular relaxation time ( $\tau$ ) for the HPMC-PEG films.

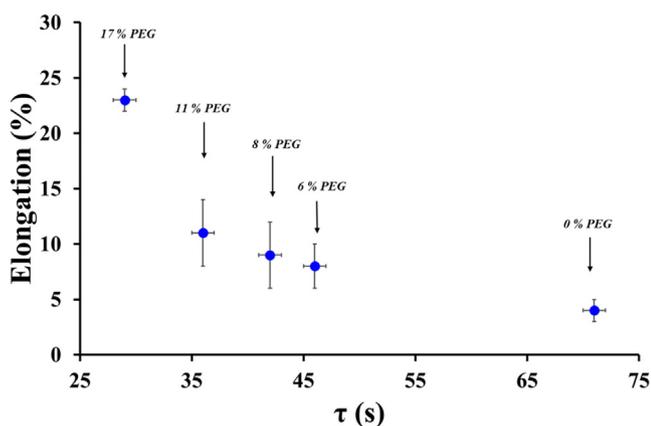


Fig. 10. A plot of the relationship between tensile elongation and molecular relaxation time ( $\tau$ ) for the HPMC-PEG films.

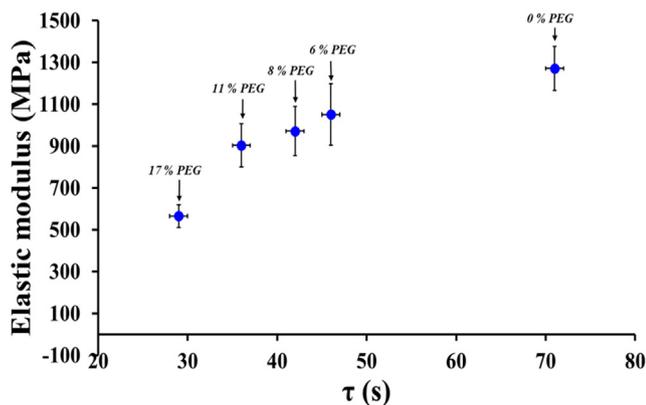


Fig. 11. A plot of the relationship between elastic modulus and molecular relaxation time ( $\tau$ ) for the HPMC-PEG films.

(Fig. 9). Tensile elongation was found to decrease with increasing  $\tau$ , while the elastic modulus increased with increasing  $\tau$  in a non-linear fashion for both parameters (Figs. 10 and 11). This again demonstrates a clear link between values obtained for molecular mobility (TSC data) and mechanical properties. Materials with lower molecular relaxation times will have lower resistance to imposed stress i.e. they are able to easily and quickly respond to the uniaxial tensile deformation stress, resulting in lower tensile strength and greater tensile elongation. On the other hand, materials with higher molecular relaxation times will exhibit greater resistance to the imposed uniaxial deformation stress, as

they are stiffer and unable to follow imposed stress as easily/quickly as those with lower molecular relaxation times. The link between parameters of molecular mobility as measured by TSC and the mechanical properties, defined by tensile analysis, indicate that materials with lower relaxation times are likely to exhibit greater flexibility when subjected to brief and low stresses. However, they will easily succumb to increasing and prolonged stresses, and are more likely to quickly change from elastic to plastic deformation.

The increase in tensile strength and elastic modulus, and decrease in tensile elongation as a function of  $\tau$ , demonstrates that these localized segmental mobilities detected by TSC, are major contributors to the mechanical properties of plasticized HPMC films. It is shown that decreasing molecular relaxation time, by means of plasticizer, reduces the stiffness parameter (elastic modulus) and the strength of the film. Decreasing relaxation time i.e., an increase in molecular mobility, is also an indication of increased degrees of motional freedom for the HPMC molecules. This is caused by the disruption of the stronger HPMC inter-molecular interactions by PEG molecules, which in turn limits closer packing of the HPMC molecules, resulting in increased free volume, making it easy for molecules to slip past each other. It is by this same process that the tensile strength and elastic modulus are also reduced.

The trends observed demonstrate the complexity of the relationships between molecular mobility and tensile properties. The knowledge gained from these relationships provide opportunities to understand and potentially optimize polymer films, but also highlights challenges associated with optimizing mechanical properties of film based formulations. Since the interdependence of the parameters of tensile properties of plasticized HPMC films on mobility differ, it is possible to optimize the tensile property of interest at the molecular level. However, the ability to do this is challenging, since it is not possible to change one parameter without impacting another with completely different dependence on the magnitude of change. For example, below a  $\tau$  value of 45 s, a small change in  $\tau$  is accompanied by a sharper change in tensile elongation and elastic modulus compared to tensile strength.

#### 4. Conclusions

TSC has been used to characterize the glassy state molecular mobility of HPMC polymer films, with varying levels of PEG content (0–17% w/w). PEG was shown to decrease the molecular relaxation temperature and time. The mobility observed in these films was of a cooperative nature. This was unexpected given that the relaxations observed were so far below the  $T_g$ , and had such low associated heat energy, that they could not be detected by DSC. Such an observation demonstrates, for the HPMC films, that considerable molecular mobility exists well below room temperature, which can have major physical and chemical stability implications. The relationship between molecular relaxation parameters ( $T_g'$  and  $\tau$ ),  $T_g$  and tensile properties have been empirically demonstrated. It was found that  $T_g$  was linearly related to molecular relaxation time ( $\tau$ ) and the  $T_g'$  (relaxation peak temperature) with an  $r^2$  of  $> 0.97$ . It has been shown that increasing molecular relaxation time within the glassy state decreases the  $T_g$ . Tensile strength was also found to be linearly related to molecular relaxation time with an  $r^2$  value  $> 0.98$ , in which increasing molecular relaxation time increased tensile strength. A completely different relationship was observed for tensile elongation and elastic modulus. These two mechanical parameters had a non-linear relationship with molecular relaxation time. Increasing molecular relaxation time decreases tensile elongation until a certain point (45 s), such that a further increase in relaxation time has little impact on elongation. Similar behavior was observed for elastic modulus, except in this case elastic modulus increased with molecular relaxation time.

The data presented in this work empirically demonstrates the complex nature of the relationship between molecular mobility,  $T_g$  and

tensile properties for plasticized HPMC films. Whilst these findings agree with the general inference that increased molecular mobility is the cause of a decrease in  $T_g$ , tensile strength and elastic modulus and the increase in elongation for plasticized polymeric films, it highlights that the dependence of these bulk parameters on molecular mobility differ greatly. Therefore, empirical measurement of molecular mobility parameters is important to fully understand and predict the thermo-mechanical behavior of polymeric films. TSC has proved to be a vital technique in characterizing glassy state molecular mobility. Knowledge gained from this technique is very useful for stability and performance ranking, and offers the opportunity to predict the behavior of materials using data generated at or below typical storage conditions.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpx.2019.100033>.

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