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

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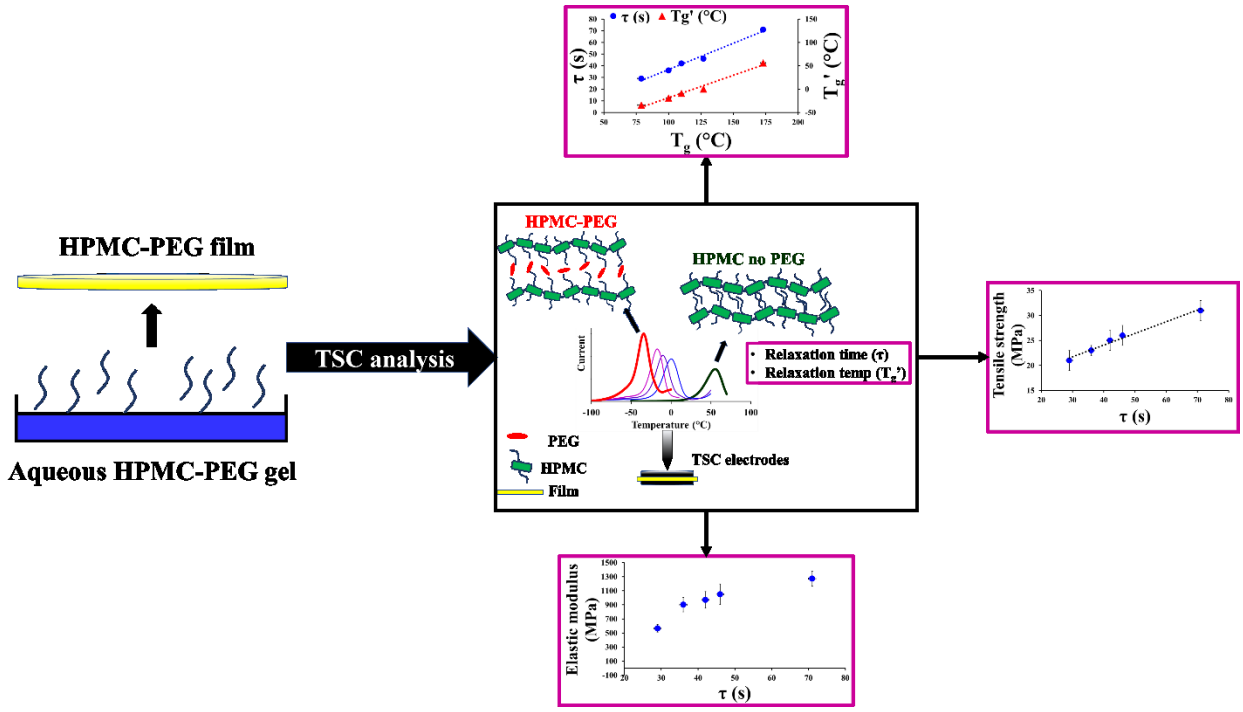
ABSTRACT

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. Here 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. Parameters of molecular mobility (molecular relaxation time and temperature) were determined by Thermally Stimulated Current Spectroscopy (TSC). The tensile properties and T_g of the HPMC films were determined by Texture Analyzer and DSC, respectively. Molecular mobility detected by TSC were cooperative and occurred at temperatures (T_g') well below (113 to 127°C below) the bulk T_g. The relaxation times (τ) were 71 ± 1, 46 ± 1, 42 ± 1, 36 ± 1 and 29 ± 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 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 on molecular mobility and its influence on bulk level properties of materials. Data generated from TSC proves 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.

GRAPHICAL ABSTRACT



KEYWORDS:

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Molecular mobility

Mechanical properties

Relaxation time

Polymer films

Capsules

Glass transition

1.0 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 development of polymer films for pharmaceutical applications.

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 the lowering of the T_g and elastic modulus (Honary and Orafai, 2002; Daniels, 2009). In addition, the molecular weight of plasticizers has also been shown to be a factor in plasticizer efficiency (Honary and Orafai, 2002).

Several theories exist, explaining the mechanism by which plasticizers change 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 in 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 mobility of confined polymers for several fields of application i.e. microelectronic, optoeletronics 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. α-relaxation that is associated with the glass transition and the subtler secondary relaxations (β and γ 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, 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 (β) is applied from T_0 to a final temperature (T_f) that is higher than the T_p.

The second experiment, the TW, deconvolutes 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 global TSDC signal. Each polarization is followed with a depolarization step, where the relaxation modes with the fastest relaxation time is 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.

2.0 EXPERIMENTAL

2.1 Materials

Hydroxypropyl methylcellulose (HPMC) (average molecular weight ~ 860 kDa, viscosity of 1% aqueous solution at 20°C is ~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 hours 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 hours. The resultant films were stored in a desiccator over silica for two days before analyzing. 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 ± 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 the Q5000 IR (TA Instruments, UK). Sample mass of 3.2 ± 0.5 mg was used for all compounds. Samples were subjected to a heat-cool-heat experiment 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 with a Q2000 (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 mass of 2.60 ± 0.24 mg was heated to 140 °C to remove moisture, equilibrated at -90 °C, held isothermally for 5 minutes and heated to 200 °C at 10 °C/min.

186

187 **2.2.4 Texture analysis**

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

194

195 **2.2.5 Thermally stimulated current (TSC) experiments**

196 TSC studies using the thermally stimulated depolarization current (TSDC) experiment, covering
197 the range -100 to 70 °C were conducted with a TSCII/RMA spectrometer (SETARAM, France)
198 equipped with a 900 series LN2 (Liquid Nitrogen) micro-dosing cooling system (Norhof,
199 Netherlands) and 6517A electrometer (Keithley, USA). Experiments were performed using
200 electrode arrangement that consists of bottom (13 mm diameter) and upper (10 mm diameter) steel
201 electrodes. The sample diameter of the film cut for analysis was 12.0 ± 0.5 mm and the surface
202 area of the sample in direct contact between the top and the bottom electrode was 78.54 mm^2. The
203 analysis chamber was evacuated to 10^{-4} mbar and flushed several times with high purity helium
204 (1.1 bar) prior to analysis. Each sample was initially subjected to a pre-treatment in which it was
205 heated to 60 °C (the film forming temperature) and held isothermal for 30 min. This was followed
206 by evacuation of the analysis chamber to 10^{-4} bar and flushing three times with high purity helium
207 (1.1 bars). The global TSDC signals were obtained by polarizing the sample at 60, 5, -5, -12, and
208 -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.

3.0 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 Figure 1, the second heating profile was practically flat, indicating complete removal of water from the films when heated to 150 °C.

The DSC data presented in Figure 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 increased degree of molecular mobility i.e. molecules of plasticized films in the glassy state exhibit increasingly higher state of mobility and therefore kinetic energy, with increasing plasticizer content. This presents a problem in detecting 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 thermo-responsive properties of Eudragit RS films. In their work T_g data could not be provide for Eudragit RS film plasticized with 20 % triethyl citrate (TEC) plasticizer, because it could not be detected on the DSC. This impacts the ability to make 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).

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.

253 **Table 1.** Summary of the tensile strength, percent elongation at break and elastic modulus of
254 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

255

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

267

268 **3.3 Thermally Stimulated Depolarization Current (TSDC)**

269 For this study only the initial global TSDC peak detected for each sample was considered. There
270 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). 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 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. 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 HPMC and PEG molecules. Figure 3 shows typical output of these TSDC experiments. Increasing PEG concentration (% w/w) was found to decrease the temperature of

molecular dipole relaxation (Figure 4). The relaxation peak temperature (T_m) of the un-plasticized HPMC film was detected at 56.0 ± 0.7 °C, whilst films containing 6, 8, 11 and 17 % (w/w) PEG were observed at -0.3 ± 0.8 °C, - 9.0 ± 1.1 °C, -18.6 ± 1.4 °C and -33.8 ± 1.0 °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 (Figure 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 processes. As shown in Figure 6, all the PEG plasticized HPMC films exhibit two groups of discrete relaxation processes within temperature range of analysis. The first group (lower temperature grouping) corresponds to the global relaxation process identified in the TSDC investigations. The second group of relaxations were part of the infinitely increasing TSDC signal (section B of the supplementary). It was not possible to assess the existence of this second group of relaxations for the HPMC films with no PEG as heating these samples above 70°C was suspected to cause a change to the nature of the material (and hence

317 mobility) in subsequent experiments. Both groups of discrete relaxation processes, only identified
318 in the HPMC films containing PEG, increased with increasing PEG content. However, the relative
319 intensity of the second group of discrete relaxation processes (relative to the first group of discrete
320 relaxation processes) appeared to increase more in line with the increase in PEG concentration.
321 This implied that this group of relaxations mostly originated from the movement of PEG
322 molecules, and were assigned to the increased number of mobile dipoles in PEG molecules
323 compared to HPMC molecules. The current signals associated with these processes were very
324 noisy and inconsistent, due to contributions from space and interfacial charges. As a result, it did
325 not form part of the discussion in this work.
326
327 The inserts in Figure 6 show the distribution of relaxation times (τ), referred to as the Bucci lines,
328 for each discrete relaxation process. Straight Bucci lines generally indicate narrowly distributed
329 activation energies, and imply a single mode of molecular relaxation e.g. twisting of polymer end
330 group or orientation of a single fragment of the polymer chain. Bucci line curvature, on the other
331 hand, suggests activation energies are not narrowly distributed, therefore each 'discrete' relaxation
332 process may in fact contain two or more different modes of molecular orientations (Alvarez et al.,
333 2000; Correia et al., 2000; Diogo and Ramos, 2008; Viciosa et al., 2010). This suggests activation
334 of two or more groups of molecular fragments with different activation energies. In this study the
335 Bucci lines obtained for the first group of relaxation processes, were generally found to be straight.
336 Each Bucci line was fitted with the Eyring equation to determine the enthalpy of activation ($\Delta H^{\ddagger}$
337), entropy of activation ($\Delta S^{\ddagger}$) and Gibbs free energy of activation ($\Delta G^{\ddagger}$). More details on the
338 determination of these parameters along with the relaxation time (τ) are provided in section A of
339 the supplementary.

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 Figure 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 (β- and γ-relaxations) and the cooperative primary relaxations (α-relaxation). The un-plasticized HPMC films and the PEG plasticized HPMC films were found to deviate from the zero-entropy predictions, which implied 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 high enough energy that is detectable in DSC experiments. This level of cooperativity was observed at higher temperatures (>70 °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 of too low 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

363 viscous/heat changes in the bulk material to generate a sufficiently large signal to be detected by
364 DSC. These low energy cooperative relaxations are likely to arise mostly from the orientation of
365 the hydroxypropyl methyl side chains and small units of the HPMC end groups, facilitated by the
366 cooperative orientation of PEG molecules. The TSDC peak temperature (T_m) of these cooperative
367 molecular relaxations is denoted T_g' from here on.
368
369 Cooperative molecular relaxations or α-relaxations, are typically associated with the bulk glass
370 transition and expected to be present at or near the T_g (Ramos and Mano, 1997; Ramos et al., 2004;
371 Smith and Bedrov, 2007; Diogo and Ramos, 2008; Pinto et al., 2010). Data presented in this study
372 demonstrates that this is not the case for all materials. For the HPMC films analyzed, cooperative
373 mobility occurs well below the T_g (between 113 to 127 °C below the T_g) where localized, low
374 energy molecular relaxations occur. Such information is pertinent for understanding stability
375 implications of plasticized drug loaded polymeric films, where such mobility could result in
376 polymer-drug phase separation and/or crystallization of an amorphous drug dispersions.
377 Furthermore, understanding molecular mobility in materials at temperatures below or around their
378 storage conditions can allow for a better prediction of stability and performance ranking, in
379 addition to offering opportunity to optimize materials performance at the molecular level.
380

381 **3.5 Relationships between molecular mobility, T_g and mechanical properties**

382 The molecular relaxation time (τ), T_g' and the T_g for the samples analyzed are presented in Table
383 2. The relaxation time determined in this study is a measure of the time scale of the cooperative
384 molecular relaxations associated with the T_g', and is therefore a direct measure of molecular

385 mobility in the glassy state. The fact that both T_g' and τ decreased with increasing PEG content,
386 demonstrates that PEG enhances the ease and rate of molecular mobility in the HPMC films.
387
388 **Table 2** Data for the cooperative relaxation TSDC peak temperature (T_g'), relaxation time (τ), for
389 the highest intensity TW output, and bulk glass transition tempetaure (T_g) obtained for the HPMC
390 films.

% PEG content (w/w)	T_g' (°C)	T_g (°C)	τ (s)
0	56 ± 1	173 ± 2	71 ± 1
6	0 ± 1	127 ± 1	46 ± 1
8	-9 ± 1	110 ± 2	42 ± 1
11	-19 ± 1	100 ± 2	36 ± 1
17	-34 ± 1	79 ± 3	29 ± 1

391
392 The influence of plasticizers on T_g and tensile properties is typically linked to molecular mobility,
393 usually with no empirical evidence. As such, the nature of the relationship between mobility, T_g
394 and tensile parameters is not always clear. Data generated from TSC in this study have identified
395 several important trends between molecular mobility and physico-mechanical properties. For
396 example, τ and T_g' were found to be linearly related to T_g (Figures 8). The lower the τ or T_g' the
397 lower the T_g, and vice versa. This shows that mobility at low temperature regions of the glassy
398 amorphous films (TSC data), are directly related to the glass transition process observed at a much
399 higher temperature in DSC.
400

401 The tensile strength of the plasticized HPMC films was also found to be linearly related to τ i.e.,
402 tensile strength increases as τ increases (Figure 9). Tensile elongation was found to decrease with
403 increasing τ, while the elastic modulus increased with increasing τ in a non-linear fashion for both
404 parameters (Figures 10 and 11). This again demonstrates a clear link between values obtained for
405 molecular mobility (TSC data) and mechanical properties. Materials with lower molecular
406 relaxation times will have lower resistance to imposed stress i.e. they are able to easily and quickly
407 respond to the uniaxial tensile deformation stress, resulting in lower tensile strength and greater
408 tensile elongation. On the other hand, materials with higher molecular relaxation times will exhibit
409 greater resistance to the imposed uniaxial deformation stress, as they are stiffer and unable to
410 follow imposed stress as easily/quickly as those with lower molecular relaxation times. The link
411 between parameters of molecular mobility as measured by TSC and the mechanical properties,
412 defined by tensile analysis, point out that materials with lower relaxation times are likely to exhibit
413 greater flexibility when subjected to brief and low stresses. However, they will easily succumb to
414 increasing and prolonged stresses, and are likely to quickly change from elastic to plastic
415 deformation.
416
417 The increase in tensile strength and elastic modulus, and decrease in tensile elongation as a
418 function of τ, demonstrates that these localized segmental mobilities observed in the TSC, are
419 major contributors to the mechanical properties of plasticized HPMC films. It is shown that
420 decreasing molecular relaxation time, by means of plasticizer, reduces the stiffness parameter
421 (elastic modulus) and the strength of the film. Decreasing relaxation time i.e. increase rate of
422 molecular mobility, is also an indication of increased degrees of motional freedom for the HPMC
423 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 τ value of 45 s, a small change in τ is accompanied with a sharper change in tensile elongation and elastic modulus compared to tensile strength.

4.0 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 heat energy associated, 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 τ), T_g and tensile properties have been empirically demonstrated. It was found that T_g was linearly related to molecular relaxation time (τ) 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), where 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 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 materials behavior using data generated at or below typical storage conditions.

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650
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658 (T_g'), relaxation time (τ), for the highest intensity TW output, and bulk glass transition temperature
659 (T_g) obtained for the HPMC films.

660

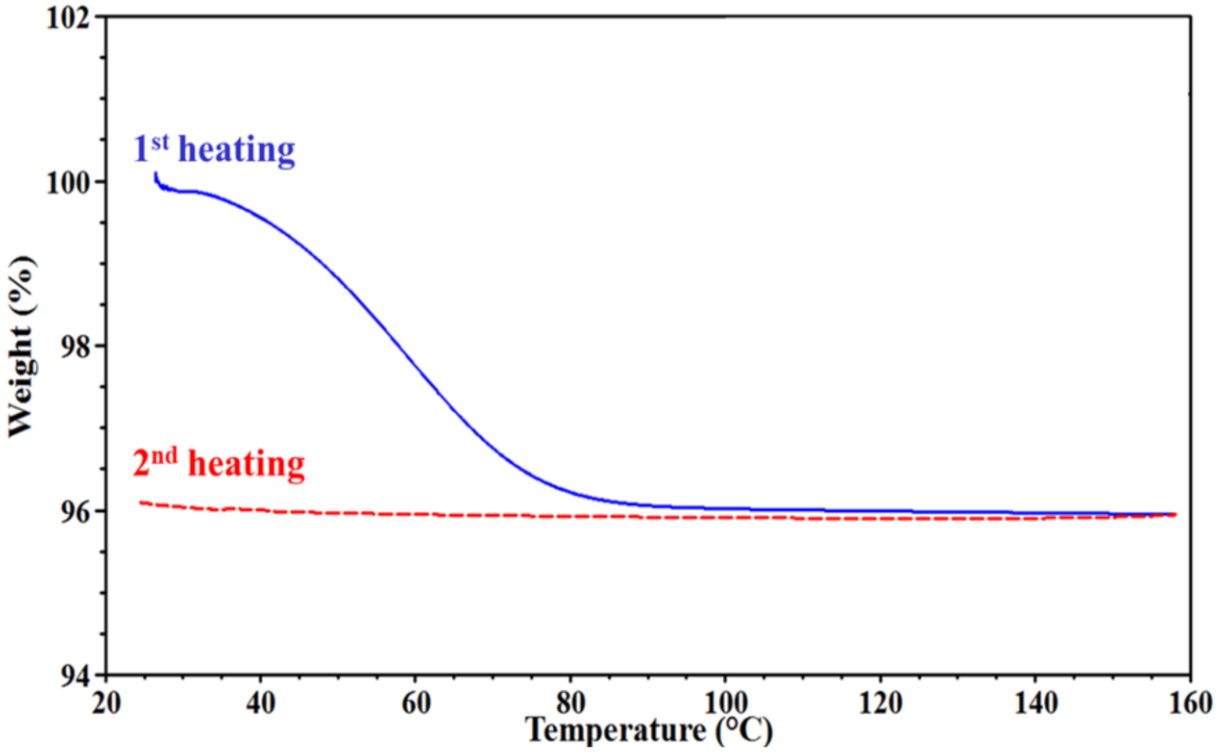
102
100
98
96
94
Weight (%)
1st heating
2nd heating
20
40
60
80
100
120
140
160
Temperature (°C)

Figure 1

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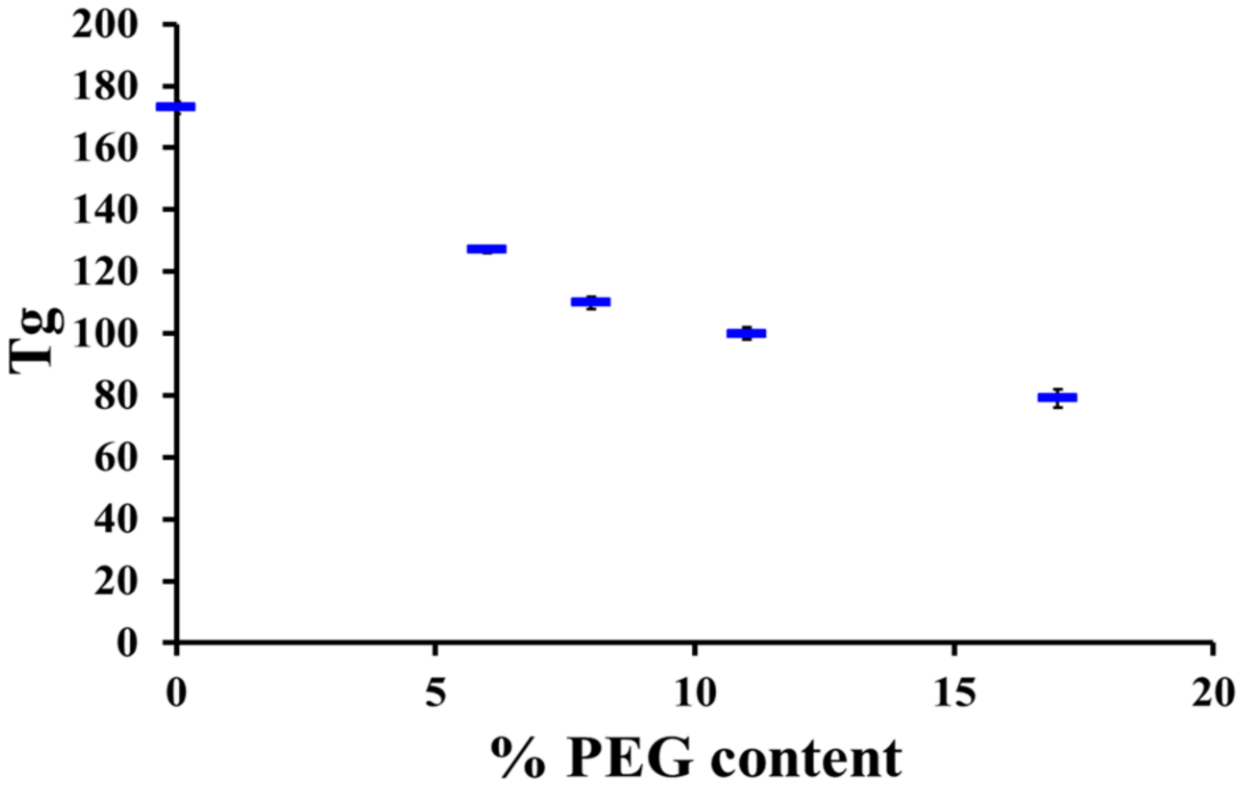

675

676 Figure 2

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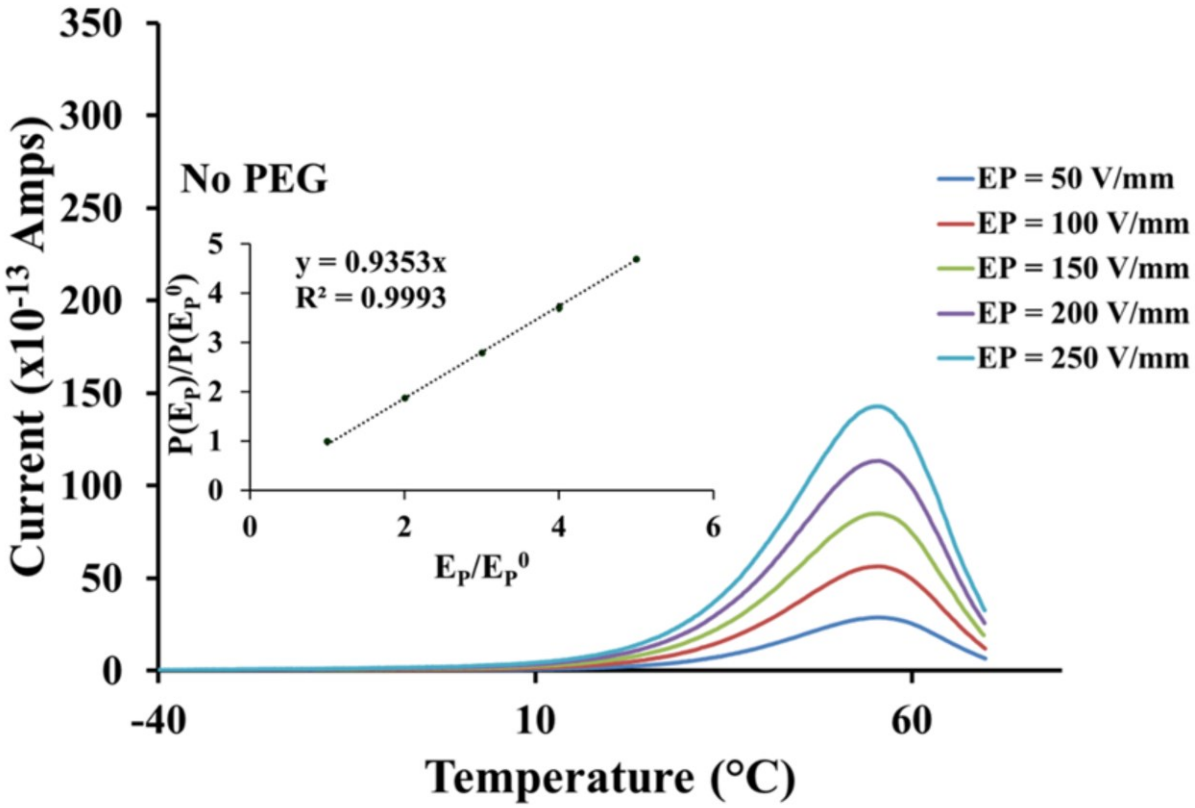
No PEG
Current (x10-13 Amps)
Temperature (°C)
EP = 50 V/mm
EP = 100 V/mm
EP = 150 V/mm
EP = 200 V/mm
EP = 250 V/mm
y = 0.9353x
R² = 0.9993
P(EP)/P(EP0)
EP/EP0

Figure 3

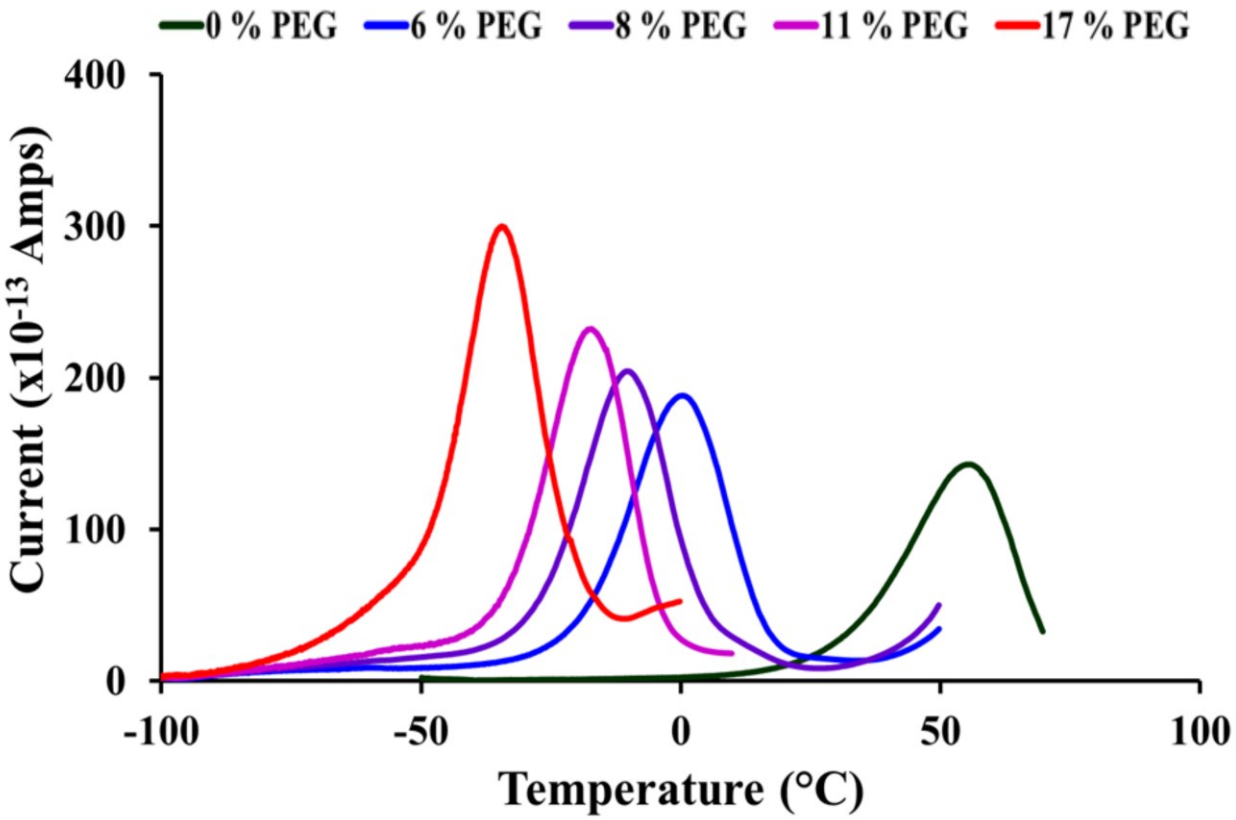
0 % PEG
6 % PEG
8 % PEG
11 % PEG
17 % PEG
Current (x10-13 Amps)
400
300
200
100
0
-100
-50
0
50
100
Temperature (°C)

Figure 4

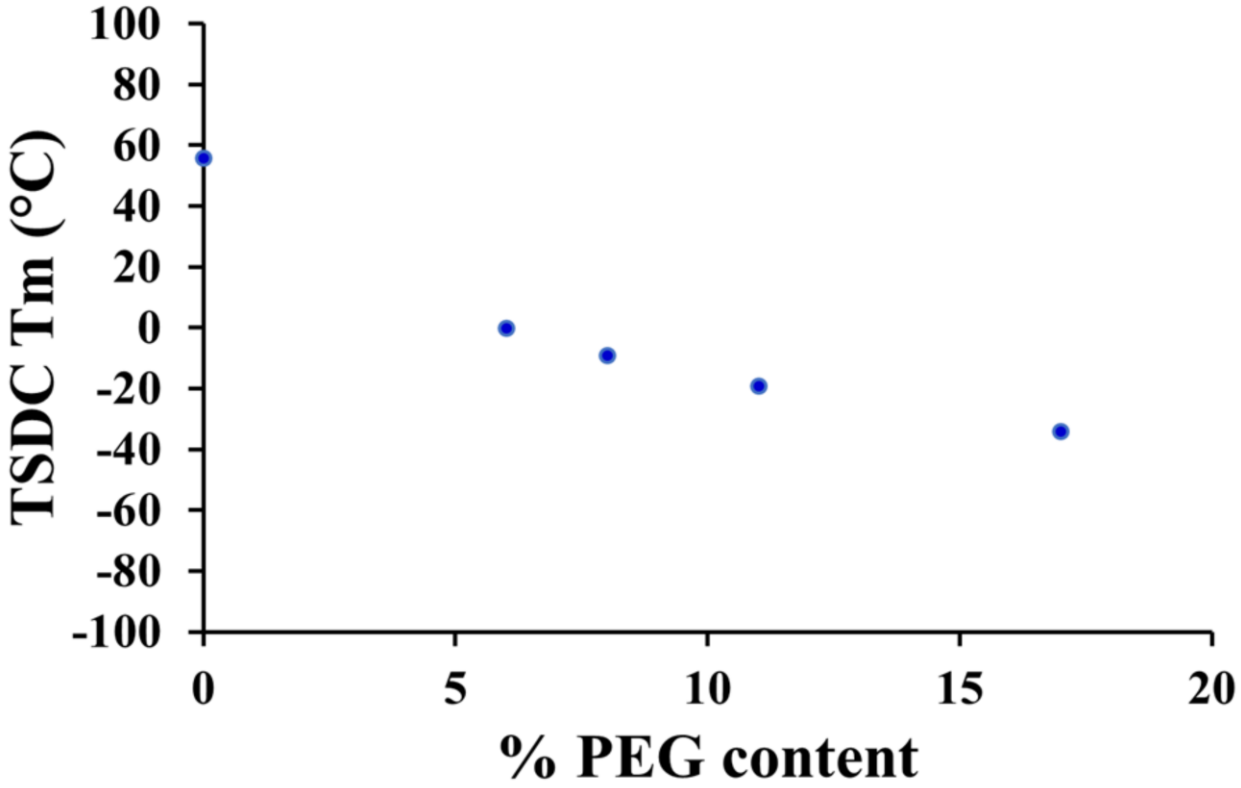

Figure 5

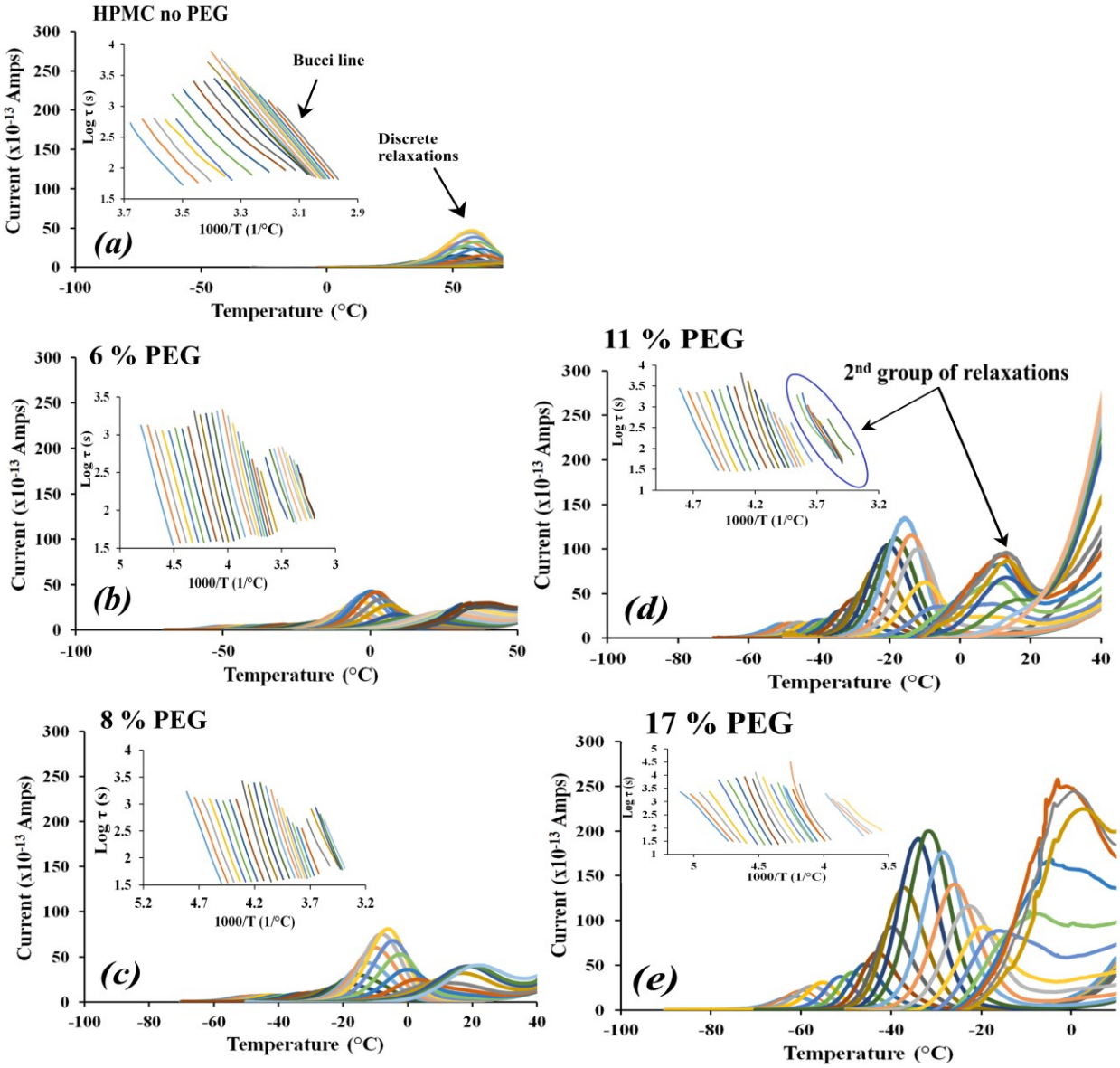
HPMC no PEG
Bucci line
Discrete relaxations
(a)
Current (x10-13 Amps)
Temperature (°C)
Log τ (s)
1000/T (1/°C)
6 % PEG
(b)
11 % PEG
2nd group of relaxations
(d)
8 % PEG
(c)
17 % PEG
(e)

Figure 6

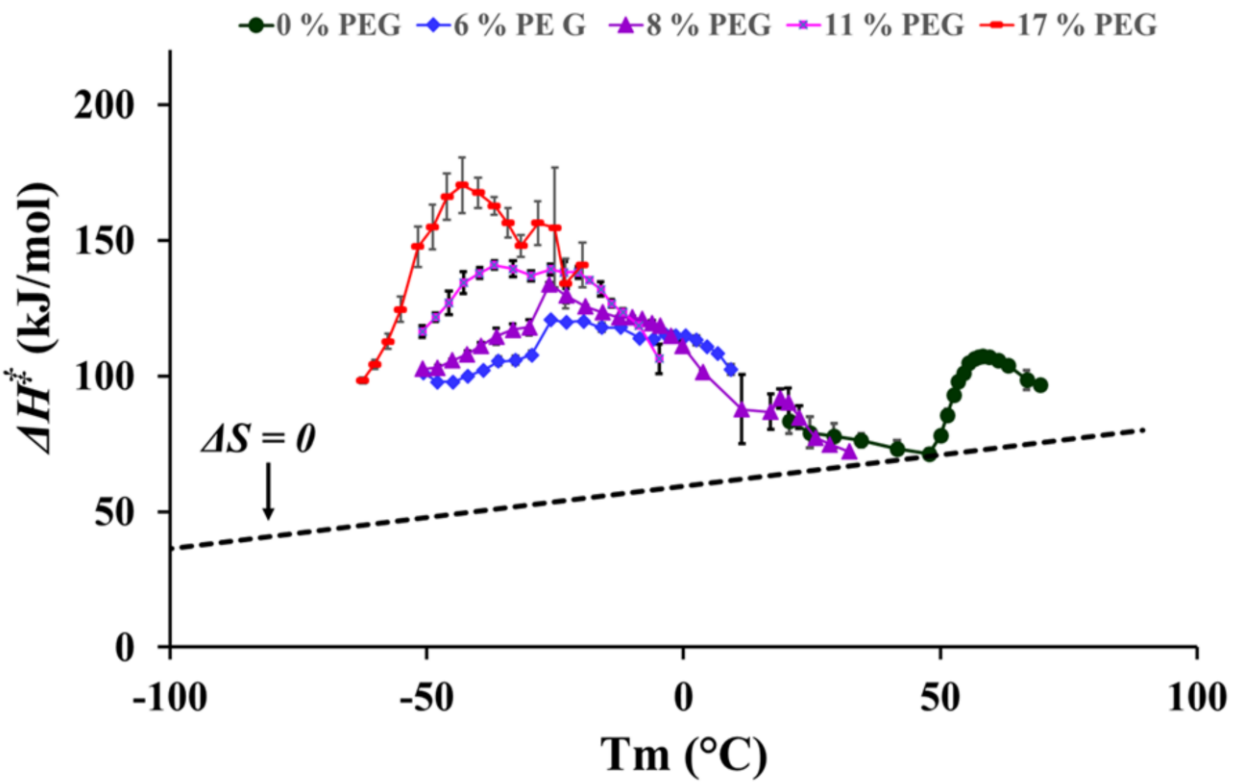
0 % PEG
6 % PE G
8 % PEG
11 % PEG
17 % PEG
200
150
100
50
0
ΔH‡ (kJ/mol)
ΔS = 0
-100
-50
0
50
100
Tm (°C)

Figure 7

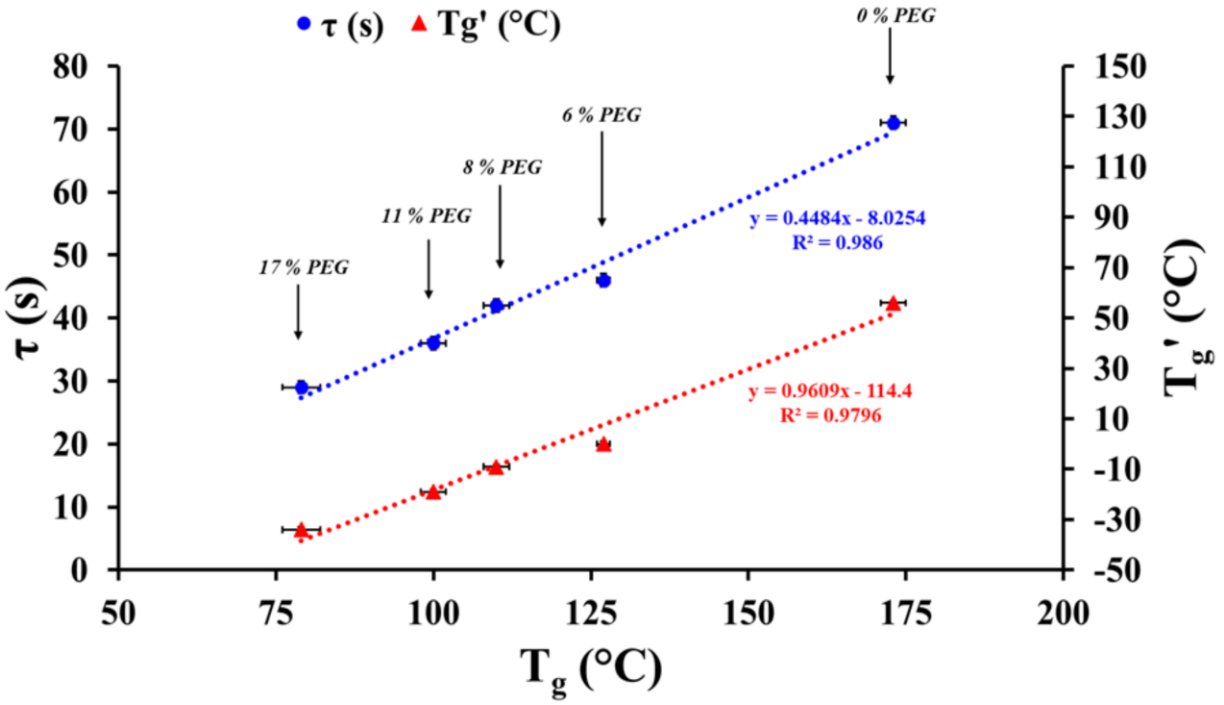
τ (s)
Tg' (°C)
0 % PEG
6 % PEG
8 % PEG
11 % PEG
17 % PEG
y = 0.4484x - 8.0254
R² = 0.986
y = 0.9609x - 114.4
R² = 0.9796
τ (s)
T g ' (°C)
T g (°C)
80
70
60
50
40
30
20
10
0
150
130
110
90
70
50
30
10
-10
-30
-50
50
75
100
125
150
175
200

Figure 8

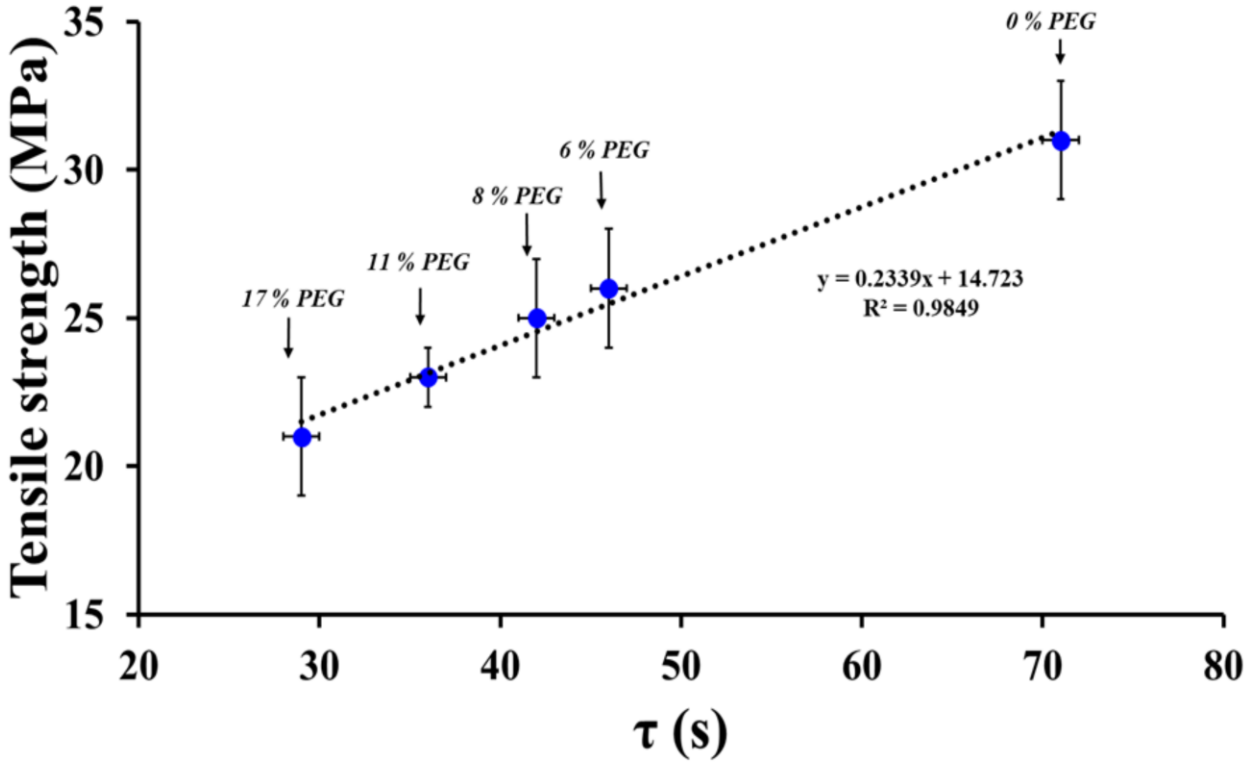
Tensile strength (MPa)
τ (s)
17 % PEG
11 % PEG
8 % PEG
6 % PEG
0 % PEG
y = 0.2339x + 14.723
R² = 0.9849
35
30
25
20
15
20
30
40
50
60
70
80

Figure 9

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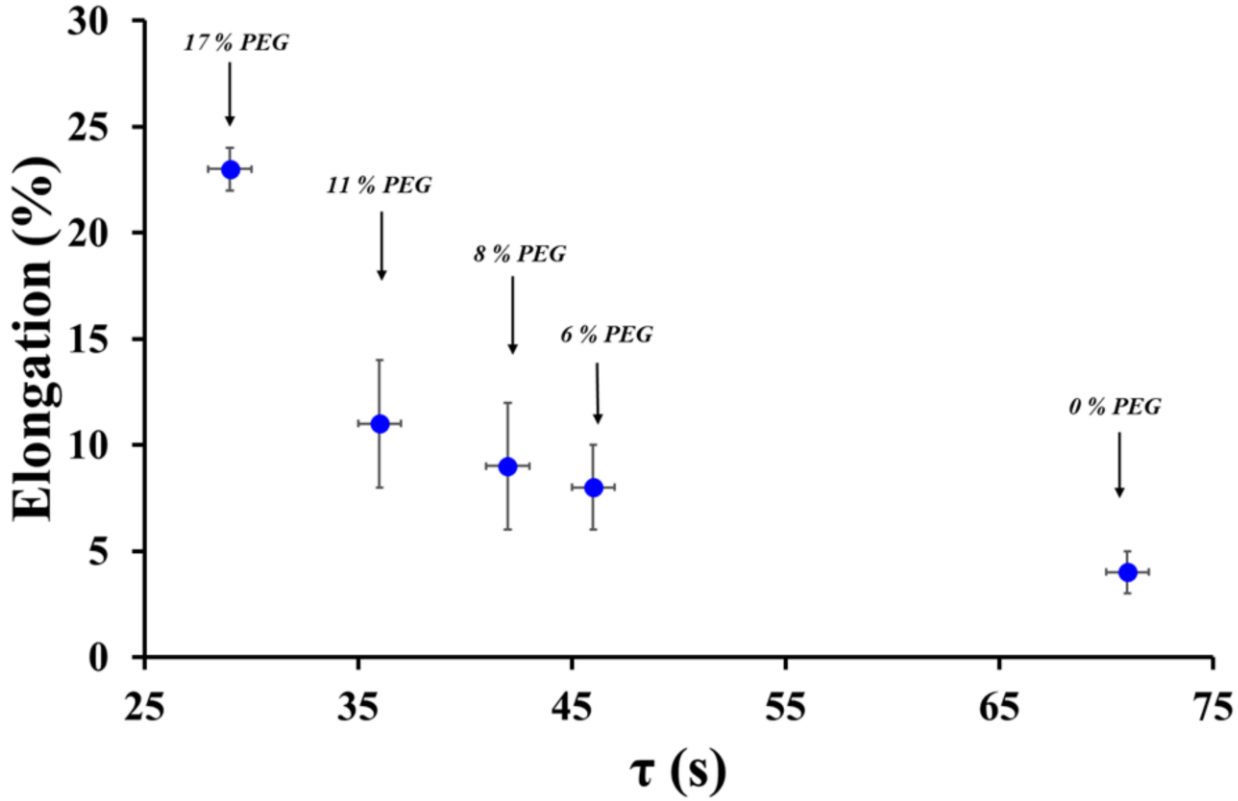

741

742 Figure 10

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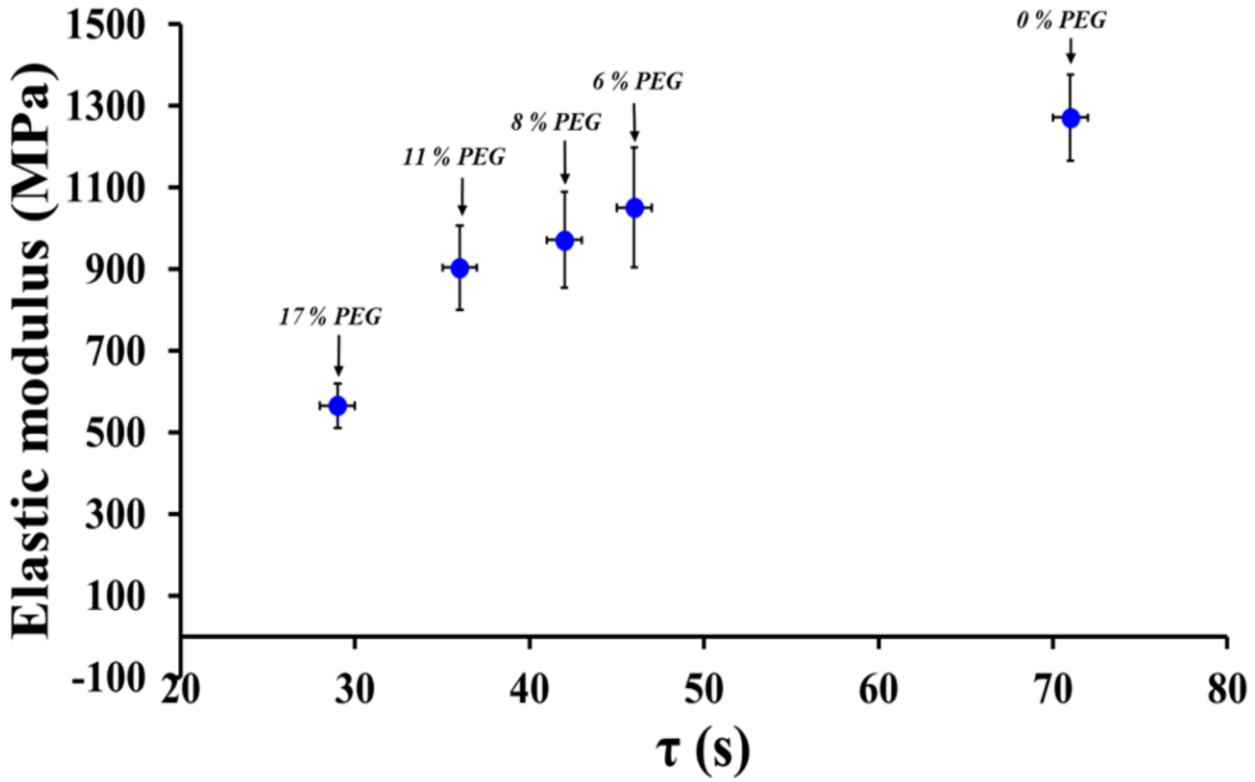

748

749 Figure 11