Molecular Mobility of Hydroxyethyl Cellulose (HEC) Films Characterised by Thermally Stimulated Currents (TSC) Spectroscopy

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 (ABSTRACT)

Molecular mobility has long been established to relate to textural properties and stability of polymer films and is therefore an important property to characterise to better understand pharmaceutical film formulations. The molecular mobility of solvent cast hydroxyethyl cellulose (HEC) films has been investigated by means of thermally stimulated current (TSC)

below the temperature at which the film was formed. Preliminary physical characterisation of the films was performed using XRPD, TGA, DSC and texture analysis (tensile properties). XRPD results showed the films to be completely amorphous with T_g determined by DSC to be $127 \pm 1°C$. TGA analysis showed the films to contain 8 ± 1 % water and film was dried to only 0.06 ± 0.01 % water content when heated to $160°C$. Application of TSC detected molecular mobility in HEC films at sub-zero temperatures. Two motional transitions with average relaxation time of 50 ± 3 s were identified; a β-relaxation at $-57 \pm 2°C$, attributed to localised non-cooperative orientation of HEC polymer chain ends and the hydroxyethyl side groups and an α-relaxation, originating from cooperative segmental mobility, at $-20 \pm 2°C$. The tensile properties i.e. elongation, tensile strength and elastic modulus of the HEC film have been related to the molecular relaxation processes detected by TSC.

1. Introduction

Polymer films are one of the most important technologies in pharmaceutical development with applications ranging from use as drug delivery systems such as Triaminic and Theraflu thin strips (Novartis), and use in controlled drug delivery such as films in enteric coated tablets to enhancing the appearance and taste of pharmaceutical products (Felton, 2007, Bhattacharjya and Wurster, 2008, Bala et al., 2013). Optimisation of these films for a particular application, however, is a challenging process and one that requires in-depth understanding of materials behaviour. It is established that mechanical (tensile) properties and stability, which are commonly characterised to evaluate formulated films, are associated with the glass transition temperature (T_g) (Fadda et al., 2010, Connie and John, 2005, McPhillips et al., 1999). The T_g (in addition to the mechanical properties and the physical and chemical stability) of polymer films have, in turn, been related to molecular mobility (Damaceanu et al., 2014, Ballesteros and Walters, 2011, Fadda et al., 2010, Bhugra et al., 2008, Zhang et al., 2013). Characterisation

of molecular mobility is therefore important to better understand polymer film performance for

pharmaceutical applications.

Various analytical techniques have been employed to investigate molecular dynamics in

polymer films. Techniques such as de-wetting (Connie and John, 2005, Wang and McKenna,

2013), elipsometry (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 been

used to interrogate the dynamic behaviour of polymer films of varying thickness on solid

support or free-standing. The application of these techniques have, collectively, demonstrated

significant decrease in T_g with decreasing film thickness below 75 nm (Connie and John, 2005,

Lipson and Milner, 2010). For films analysed on solid support, decreasing the film thickness

further to below 20 nm causes an increase in T_g (Yin et al., 2013). The decrease in T_g for films

>20 and <75 nm were shown to have no corresponding enhancement in polymer chain mobility

and the increase in T_g for films < 20 nm thick were attributed to reduction of segmental mobility

due to enhanced interaction between polymer segments and the solid support (Connie and John,

2005, Yin et al., 2013).

Investigation of films at such small thickness scales is important and provides interesting

information on mobility of confined polymers, which has important implications in several

fields such as microelectronics, optoelectronics, and miniature chemical and biological sensors

(Pique et al., 2003, Hojati-Talemi et al., 2013). However, the thickness of pharmaceutical films

are typically above 250 nm (May et al., 2010, May et al., 2011, Zhong et al., 2009) and the

behaviour of confined polymers at thickness < 75 nm has not been related to the bulk properties of polymer films for pharmaceutical applications. It is therefore equally important to investigate motional behaviour of polymers in bulk films.

The study of thermally stimulated current (TSC) is a useful tool for the characterisation of molecular mobility in polymer films. The technique measures currents generated by the movement of dipoles in response to an externally applied static electrical field (see Appendix A). Due to its low equivalent frequency TSC exhibits greater sensitivity and enhanced resolution of different relaxation processes, when compared with the most commonly used technique i.e. dielectric spectroscopy, for characterising molecular mobility. TSC investigation of formulated polymer films related to intrinsic mobility of polymer molecules within the film is limited and to the authors' knowledge, no such investigation has been performed on hydroxyethyl cellulose (HEC) films.

HEC is a non-ionic cellulose derivative with a broad variety of industrial applications such as in food products, adhesives, paints, textiles and paper (Rahmat et al., 2011, Roy and Rohera, 2002, Luner and Oh, 2001). This cellulose ether derivative has also found wide spread use in pharmaceuticals as controlled release matrix, binders, stabilisers, thickeners and film formers for drug coating and delivery (Kamel et al., 2008). Among the good film forming cellulose ether derivatives, HEC films are perhaps the least investigated and find use only in combination with other polymers (Morales and McConville, 2011). As such the physical behaviour of HEC polymer films has not been fully characterised when compared with other cellulose ether derivatives such as HPC and HPMC. It is therefore necessary to enhance current knowledge of the physical behaviour of HEC films for pharmaceutical applications. In this study, the molecular mobility of HEC films prepared by the solvent casting method has been characterised by means of TSC below the temperature at which the film is formed, as this best represents polymer behaviour within typical pharmaceutical application conditions.

2.   Materials and methods

2.1   Materials

Hydroxyethyl cellulose (average molecular weight ~ 250 kDa, _viscosity of 1% aqueous solution at 20°C is ~145 mPa) was purchased from Sigma Aldrich (UK).

2.2   Methods

2.2.1   Preparation of films

Films were prepared using the solvent casting method. Aqueous gel (2 % w/w) was prepared by mixing the appropriate amount of HEC in deionised 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 analysing. The films that were optically clear with no visible defects were chosen for analysis (Fig. 1). The thickness of the films were determined using a digital calliper and found to be 0.085 ± 0.005 mm.

Figure 1 here

2.2.2   Thermogravimetric analysis (TGA)

TGA studies were performed using the Q5000 IR (TA instruments, UK). Sample mass of 3.20 ± 0.5 mg was used for all compounds. Samples were heated under a nitrogen atmosphere at a flow rate of 25 ml/min from ambient temperature to 600 °C in hermetically sealed aluminium pans with a single pin hole in the lid, at a heating rate of 10 °C/min.

2.2.3   Differential scanning calorimetry (DSC)

DSC studies were performed using Q2000 (TA instruments, UK) under a nitrogen atmosphere at a flow 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.

2.2.4 Texture analysis

Mechanical (tensile) properties of the HEC films were analysed using a TA HD *plus* (Stable

Micro System, UK) texture analyser. The films ($n = 3$) devoid of any physical defects were cut

into dumb-bell shape. 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.

2.2.5 Thermally stimulated current (TSC) spectroscopy

TSC studies using the thermally stimulated depolarisation current (TSDC) mode, covering the

range -100 to 60 °C were conducted using 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 cut for analysis was 12.0 ± 0.5 mm with an average

weight of 14.7 ± 1 mg and surface area of the sample in direct contact between the top and the

bottom electrode was 78.54 mm^2. The analysis chamber was evacuated to 10^{-4} mbar and

flushed several times with high purity helium (1.1 bars) 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} and flushing three times with high purity helium (1.1 bars). The global TSDC

spectra were obtained by polarising the sample at -20 °C with a polarisation field (E_p) ranging

from 50 to 300 V/mm in increments of 50 V/mm for 2 min (t_p). In the case of thermal

6

windowing experiments (TW), samples were polarised with E_p = 250 V/mm at T_p of -86 to -8

°C in increments of 3 °C. 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   Preliminary physical characterization

Water content determined by TGA (Fig. 2) was found to be 8 ± 1 % after the dehydration

process in the initial heating to 160 °C. The sample was then cooled and reheated to 160 °C

and was found to contain only 0.06 ± 0.01 % moisture which could be attributed to bound water

within the polymeric film matrix. DSC analysis (Fig. 3) showed a single glass transition

temperature at 127 ± 1 °C, followed by degradation of the polymer at ~180 °C. The T_g

determined for the HEC films is in agreement with previously reported data (Kararli et al.,

1990). The results obtained from texture analysis show the solvent cast HEC film undergo 9 %

elongation at break, with tensile strength of 10 ± 3 Nmm^2 and elastic modulus of 115 ± 1 mPa.

Figure 2 here

Figure 3 here

3.2   TSDC

TSDC experiments were initially performed at various poling temperatures (from -80 to 50 °C)

to identify the temperature region where samples display observable and reproducible

depolarisation currents. The TSDC outputs showed that HEC films undergo a global relaxation

process with a small shoulder on the high temperature side, prior to the film forming

temperature (60 °C) (Fig. 4). This global relaxation process, which has a temperature maxima

(T_M) at -22 ± 1 °C, is confirmed to originate from molecular dipole orientations, intrinsic to

molecules in the HEC film i.e. there is a linear relationship (R^2 = 0.9998) between the ratios of

7

total polarisation (P) and that of the applied electrical field strength (E_p), with a slope very close

to unity and an intercept at 0 (Fig. 5) (Correia et al., 2000, Diogo et al., 2008, Pinto et al., 2010).

Furthermore this relaxation process was detected at the same temperature even after the sample

was dehydrated, which proves that it originates from the movement of HEC molecules within

the film with negligible or no contribution from water molecules. The increasingly high current

tail observed above 25 °C is likely to originate from a combination of polymer mobility and

movement of water molecules (which may indicate the initial molecular motions that contribute

to the evaporation process at higher temperatures).

Fig. 4 about here

Fig. 5 about here

The individual relaxation processes contributing to the global TSDC process were

deconvoluted by means of thermal windowing (TW) experiments (Fig. 6). These results show

more clearly the existence of two groups of relaxation processes with peak maxima located at

-22 ± 1 °C and 0 ± 1 °C. Furthermore, Fig. 6 (insert) shows the distribution of relaxation times

(Bucci lines) for the first twelve isolated relaxation processes to exhibit straight lines, while a

small degree of curvature was observed for rest of the isolated relaxation processes. This

indicates that up to the twelfth isolated processes (T_p = -53 °C), the activation energies of

molecular relaxations are narrowly distributed (Alvarez et al., 2000, Correia et al., 2000) and

implies the movement of a single molecular fragment for each isolated relaxation process. At

polarisation temperatures above -53 °C, Bucci line curvature observed suggests the activation

energies are no longer narrowly distributed, therefore two or more groups of molecular

fragments with different activation energies are activated in each isolated relaxation process.

These observations demonstrate that a number of motional modes are activated in HEC films

well below ambient temperatures with an average relaxation time of 50 ± 3 s.

Fig. 6 about here

The cooperative nature of these isolated relaxation processes were investigated further using the enthalpy of activation ($\Delta H^{\ddagger}$) (extracted by means of the Eyring's model) in a Starkweather type analysis (Ramos and Mano, 1997) (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, whilst for cooperative relaxation processes, the $\Delta H^{\ddagger}$ values has entropic contribution ($\Delta S^{\ddagger} \neq 0$) and will therefore deviate from the zero entropy prediction. The $\Delta H^{\ddagger}$ values for the first twelve isolated relaxations processes (first twelve points) are close to the zero entropy prediction and are therefore non-cooperative. The group of non-cooperative relaxations are secondary, β-relaxations, with the temperature located at -57 ± 2 °C. This β-relaxation is proposed to originate from localised orientation of short sections of the HEC polymer chain ends and/or the hydroxyethyl side groups.

Relaxation processes activated above -53 °C (points 13 to 27 in Fig. 7) deviated from the zero entropy line and are therefore cooperative i.e. they require the cooperation of neighbouring atoms, molecules or molecular segments to move. The rise and descent of the $\Delta H^{\ddagger}$ values represent the beginning and end of a transition (Sauer and Avakian, 1992, Sauer et al., 1996), hence points 13 to 23 (Fig. 4) are considered an α-relaxation. Points 24 to 27 represents the beginning of a second cooperative relaxation processes that is related to other higher temperature processes.

Fig. 7 about here

Cooperative mobility or α-relaxations are associated with the glass transition process (Smith and Bedrov, 2007). The fact that this α-relaxation (Tm' = -20 ± 2 °C) was not detected by DSC suggests it is of low energy and likely to originate from mobility of a small group of HEC polymer segments (smaller group(s) of polymer segments in comparison to the size and number

9

of polymer segments that would typically generate heat signal large enough to be detected by DSC for bulk glass transitions) in localised regions of the film. The solvent cast HEC film, therefore has two amorphous regions with different glass transition temperatures; a local glass transition at -20 ± 2 °C (determined by TSC) and the bulk glass transition at 127 ± 1 °C (detected by DSC).

The results obtained from texture analysis indicate that the film is brittle and hard (Felton and Porter, 2013, Felton et al.). From the TSC analysis it was observed that the HEC film undergoes β-relaxation as-well-as local α-relaxation processes (local glass transition). These molecular motions are of small scale, involving only a small group of short sections of HEC polymer molecules within the film. Therefore at the temperature of testing (22 ± 2 °C) using texture analysis, molecules within the film do not have enough motional freedom/ orientational capacity to plastically deform under tensile stress before failure. This explains the very low % elongation at break of 9 %. Due to the high average molecular weight (~250 kDa) of the HEC, polymer used is able to undergo high degree of intermolecular and intramolecular interactions through hydrogen bonding. Such high degree of interaction in the HEC film limits the ability of molecules to undergo large scale mobility, making the film brittle and rigid, resulting in the high tensile strength and elastic modulus respectively. Such low flexibility could also be due in part to the absence of plasticiser and the low residual moisture content below 10 %.

The current study potentially has important pharmaceutical technology implications for film based formulations. Generally, films have low drug loading due to the reduced physical volume as a result of the thin nature and therefore effect of such low drug loadings at the molecular level is not always detectable using the traditional thermal techniques such as DSC. Therefore, detection of molecular motions using the more sensitive TSC provides an extra capability in characterising the functional performance of pharmaceutical films. It is also plausible that the

information gained from such investigations might provide complimentary information about physico-chemical stability in the apparently dry state of pharmaceutical films which always have residual levels of bound water.

4.   Conclusions

Molecular mobility can have significant influence on the stability and textural properties of polymeric films. The application of TSC has revealed two motional processes, a β- and α-relaxations, well below ambient temperatures in solvent casted HEC film. The non-cooperative β-relaxation, detected at -57 ± 2 °C originates from independent orientation of short sections of the HEC polymer chain ends and the hydroxyethyl side groups. The α-relaxation detected at -20 ± 2 °C, which could not be detected by DSC, is attributed to cooperative mobility involving a small group of short HEC polymer segments and considered a local glass transition process. The fact that this α-relaxation (Tm' = -20 ± 2 °C) was not detected by DSC suggests it is of low energy and likely to originate from mobility of a small group of HEC polymer segments in localised regions of the film and has energy signature lower than the detection limit of conventional DSC.

The bulk T_g of the solvent cast HEC polymer film was detected at 127 ± 1 °C and it can be concluded that the HEC film investigated has two amorphous regions with different motional properties. Together with texture analysis data, this study has demonstrated that the brittle and rigid nature of the solvent cast HEC (~ 250 kDa) film at the temperature studied is attributed to the fact that it can only undergo small scale, localised and low energy molecular motions. This limited orientational capacity of HEC polymers in the film matrix is the direct result of the size of the polymer and the high degree of strong intra and intermolecular hydrogen bonding it undergoes within the film.

5.   Acknowledgement

5. References

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Figure Legends

Fig. 1 Typical example of the HEC films used for studies exhibiting transparency with no visually observable defects (e.g. patches, tears or cracks).

Fig. 2 A typical TGA output for HEC film showing the first and second heating cycles.

Fig. 3 DSC thermograms of HEC films obtained using TA Instruments (UK) Q2000 DSC. Each sample is initially heated from -90 to 140 °C at 10 °C/min to remove moisture (not shown), cooled and heated a second time from -90 to 140 °C at 10 °C/min.

Fig. 4 TSDC signals obtained for HEC film at different polarisation temperatures using a field strength of 100 V/mm. The insert is a zoomed-in area of the TSDC process of interest.

Fig. 5 Global TSDC curve overlay of HEC film polarised at -20 °C using electrical field strength (E_p) of 50 – 300 V/mm with an insert of a linear regression showing the relationship between the ratios of total polarisation and the ratios of E_p applied. P (E_p) is the polarisation obtained at a particular Ep and P (E_p^0) is the polarisation obtained for the lowest E_p.

Fig. 6 Typical TW results obtained for HEC films showing the isolated motional modes along with the corresponding distribution of relaxation times/ Bucci lines (insert) detected for below the film forming temperature.

Fig. 7 Overlay of the plots of the enthalpy of activation ($\Delta H^{\ddagger}$) values obtained for each isolated relaxation process from thermal windowing (TW) experiments and the zero entropy prediction ($\Delta S = 0$).