



Characterisation of the thermal properties of ethylcellulose using differential scanning and quasi-isothermal calorimetric approaches

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ABSTRACT

The thermal behaviour of the ethylcellulose (EC), a polymer that is widely used in pharmaceutical dosage forms, has been investigated with a view to study the glass transition and higher temperature thermal events as well as to develop new approaches to characterise this complex polymer system. Samples of EC powder were studied using conventional and modulated temperature differential scanning calorimetry (MTDSC), quasi-isothermal (Qi-)MTDSC and hot stage microscopy (HSM) with simultaneous transmitted light intensity measurements. The T_g was noted at *circa* 128–130 °C, with an accompanying baseline drift associated with a temperature dependent heat capacity change. A higher temperature combined endo/exothermic event was noted at 170–190 °C. TGA studies indicated that the exotherm was associated with oxidative degradation, with the accompanying DSC data being highly dependent on the sample encapsulation method used. The endotherm was found to be kinetically hindered, as demonstrated using Qi-MTDSC; the technique also indicated that there was little evidence for reversing processes through this transition. HSM studies indicated birefringence for the sample at low temperatures which disappeared as the material temperature approached T_g but reappeared on further heating, again disappearing at *circa* 180 °C. Light intensity scans produced a profile similar to that seen for the DSC studies. It is proposed that the sample contains microcrystals composed of unsubstituted segments of the cellulose backbone. The implications of these findings for the understanding of the pharmaceutical behaviour and thermal characterisation of ethylcellulose are discussed.

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1. Introduction

Ethylcellulose (EC) is a semisynthetic cellulose derivative that has found widespread application in the food, cosmetic, insulation and pharmaceutical fields, with applications including varnishes, lipsticks, flavour fixation, food printing and cream thickening. EC is particularly widely used within the pharmaceutical field due to its wide range of practically relevant properties, including low toxicity (being one of the few organosoluble/water-insoluble polymers with FDA approval for internal use), good film forming abilities coupled with favourable mechanical strength and relatively low cost. Therapeutic applications include the control of drug release of drugs from dosage forms such as tablets via the formation of retarding coatings (Rowe et al., 1984; Frohoff-Hulsmann et al., 1999;

Oh and Luner, 1999). The water insolubility of the film results in drug release occurring via permeation through the coating rather than free dissolution from the solid state into the gastric medium, hence not only may release be slowed but may also be tailored via the addition of plasticizers and permeation controlling agents such as hydroxypropyl methylcellulose and polyvinyl alcohol (Beck and Tomka, 1996). More recently, there has been a resurgence of interest in hot melt extrusion as a means of preparing slow release pharmaceutical dosage forms, whereby a solid matrix of drug in polymer is produced by extrusion above the softening or glass transition temperature of the polymer, with ethylcellulose attracting interest as a suitable matrix polymer (Verhoeven et al., 2008; Quinten et al., 2009).

Manufacture of EC takes place via alkali etherification of cellulose using ethyl chloride. The chemical structure of EC comprises chains of anhydroglucose units linked together by oxygen bridges, with the most commonly used materials having a degree of ethoxyl substitution between 43 and 50%. The physical properties of EC are influenced by both the main chain properties such as the degree of polymerization as well as the side chain properties, including the degree of substitution and the distribution of these substituents along the polymer chain and among the C(2), C(3) and

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C(6) positions in the anhydroglucose units (Guo and Gray, 1994). The elongation, flexibility and, to a lesser extent, glass transition temperature decrease sharply with an increase in ethoxyl content, while the hardness and moisture absorption of EC decreases sharply as the ethoxyl content increases over 43–51%. EC is a highly amorphous material, although there is recognition of lyotropic liquid crystalline properties (Bheda et al., 1980). Irrespective of the application, it is essential for the operator to have a thorough understanding of the physical properties of the polymer, not only in order to understand processing properties but also a means of predicting and controlling performance parameters such as drug release behaviour. A number of studies have been performed to this effect, including rheological and thermorheological assessment (Rowe et al., 1984; Sakellariou et al., 1986; Rowe, 1992) and thermal analysis with particular focus on the glass transition (Sakellariou et al., 1985; Hyppola et al., 1996; Hjartstam and Hjertberg, 1999). EC is a strong glass former and hence the heat capacity change through T_g is relatively subtle, rendering detection of the transition difficult, although there is general consensus that the value lies around 130 °C depending on molecular weight and degree of substitution (e.g. Sakellariou et al., 1985). Associated with this is considerable uncertainty with regard to the higher temperature behaviour of the material. It is recognized that there is a complex transition at *circa* 180 °C which may manifest as a combination of an endo- and exothermic response. Previous workers have associated this event with oxidation (Dubernet et al., 1990), although the multifaceted nature of the transition remains poorly understood. Given the current and increasing importance of high temperature processing associated with this material, understanding of these thermal events remains a priority.

This investigation involves the study of both the glass transition and the higher temperature event using a range of thermal techniques including conventional and modulated temperature DSC. We also describe the use of hot stage microscopy (HSM) and associated transmitted light intensity measurements as a function of temperature. Finally, we outline the use of quasi-isothermal studies as a means of characterising both the nature and the effects of annealing on the high temperature transition. In brief, this technique involves holding the sample at a specified temperature and modulating as a function of time. By obtaining a series of such profiles as a function of temperature it is possible to build up a sophisticated profile of not only the kinetics but also the mechanism associated with a thermal event.

Overall, therefore, the aim of the investigation is to provide a study of both the glass transitional behaviour of the material and also the less well understood higher temperature transition, with associated practical implications for the high temperature processing of the material. We also further develop the applicability of quasi-isothermal MTDSC, a technique which arguably has far greater applicability as a characterisation tool than has been apparent to date, in conjunction with a range of thermal scanning approaches.

2. Materials and methods

The EC sample (Ethocel Standard 100 Premium) was supplied by the Dow Chemical Company (Midland, MI, USA) and used in powder form as received. Thermal characterisation was performed using a heat-flux TA Instruments Q1000 DSC with Refrigerated Cooling System (RCS). Three temperature calibration standards were used (benzoic acid, indium and tin). Enthalpy calibration was performed using indium. The sample mass used was 5–7 mg in pans as stated. Samples were run at least three times and Universal Analysis software (TA Instruments) was used for analysis of all DSC and TGA results. For MTDSC studies, heat capacity calibration was performed

using sapphire (aluminium oxide). The samples were run in sealed and pin-holed pans at 2 °C/min with a modulation of ± 0.212 °C over 40 s. All experiments were repeated three times to ensure reproducibility. MTDSC also allows the measurement of heat capacity under quasi-isothermal conditions, i.e. the underlying heating rate is effectively zero with the exception of small temperature modulation (Androsch and Wunderlich, 2000). Quasi-isothermal MTDSC experiments were carried out using a temperature modulation of ± 1 °C and period of 60 s, with increments as stated.

TGA was performed using approximately 10 mg of sample in open aluminium pans using a Hi-Res TGA 2950 (TA Instruments). Nitrogen or compressed air was used as the purge gas as stated and the flow rate was 60 cm³/min through the furnace and 40 cm³/min through the TGA head. The samples were heated from 30 to 300 °C, with an applied scanning rate of 2, 5 and 10 °C/min. All experiments were repeated at least three times.

EC powder was observed using a Leica DMLS microscope fitted with a Mettler Toledo FP82HT hot-stage and FP90 Central processor. The sample was heated at a ramp rate of 10 °C/min and observed in cross-polar mode; light intensity transmitted through the sample was simultaneously recorded.

3. Results

3.1. Basic thermal profile of EC

The EC sample was characterised using standard DSC in the first instance, with the objective of studying T_g as well as identification of the higher temperature transition alluded to earlier. Fig. 1 shows the heat flow signals of EC at 10 °C/min during heating, cooling and reheating in a hermetically sealed pan. This basic DSC scan revealed several key features including the baseline curvature, glass transition temperature (process A) and the endo- followed by exothermic events (process B and C respectively) between 170 and 190 °C.

EC is believed to be a highly or fully amorphous material (Sakellariou et al., 1985) and its T_g has been determined to be within the region of 130–150 °C, although the measured value appears to be dependent on the type of EC and the measurement method used. Observation of Fig. 1 clearly indicates that the T_g involves a subtle baseline change, indicating that EC is a strong glass former which exhibits limited rheological and heat capacity change through the transition, rendering it more difficult to characterise. Hyppola et al. (1996) also reported difficulty in measuring the T_g of EC films

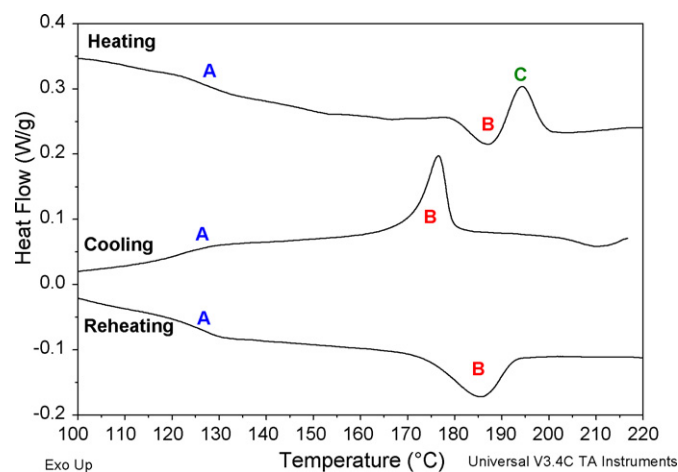


Fig. 1. DSC curve showing heat flow as a function of temperature for the heating, cooling and reheating of EC in a hermetically sealed pan at 10 °C/min (letters A, B and C denotes the thermal events under investigation; glass transition, first (endothermic) and second (exothermic) high temperature events).

using DSC, reporting that torsional braid and thermomechanical analysis were more sensitive means of assessment. The authors reported that molecular mobility increased at 60–70 °C, with maximum energy dissipation at 131.5 °C; this increased mobility may be associated with the unusually high degree of baseline drift noted in this study. This drift was found to be reproducible and a real effect of the sample, as supported by extensive baseline calibration.

The effect of heating rate was investigated and found to have a limited effect, with the T_g measured at the event midpoint as 130.9, 128.4 and 127.3 °C for 10, 5 and 2 °C/min respectively. It is also noteworthy that on recycling the material, the T_g value remains reasonably constant but the endo/exothermic response is seen as a single endothermic response on reheating. The significance of this will be discussed in the subsequent section.

3.2. Investigation into the high temperature exothermic response

Exothermic processes in polymers are usually associated either with crystallisation processes or with chemical alteration (typically crosslinking or degradation). EC is known to be prone to oxidative degradation at elevated temperatures (McBurney, 1949; Dubernet et al., 1990). Similarly, at higher temperatures embrittlement may also occur unless the polymer is protected by antioxidants; such materials may be incorporated into commercial EC formulations in order to prevent excessive degradation and to prolong mechanical performance consistency. On this basis it is logical to suggest that the observed exotherm may be associated with oxidative degradation.

Thermogravimetric analysis (TGA) may be used to study the oxidative degradation of polymers; in particular, one may change the purge gas from anhydrous nitrogen to compressed air and observe the differences in weight loss profile. These are expressed in terms of the derivative profiles for clarity. When EC was tested in the presence of oxygen (via compressed air) and nitrogen, the weight loss started 50–60 °C earlier when EC was purged with the former (Fig. 2). Heating rate had an impact on the onset temperature of degradation, with lower rates leading to lower temperature profiles, as one would expect for a kinetically hindered reaction (such as chemical degradation) as the lower rates allow more time for the process to occur during the heating process, leading to manifestation of that process at lower temperatures. From the TGA studies, therefore, it can be seen that EC is very sensitive to degradation in the presence of oxygen in the environment, which is consistent with previous studies (McBurney, 1949; Brown

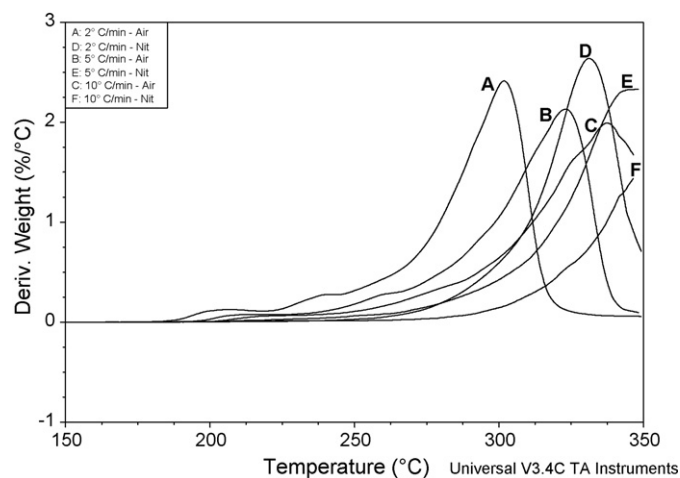


Fig. 2. Derivative-TGA curve of EC showing the onset temperature of degradation under nitrogen and compressed air at 2 °C/min (A and D), 5 °C/min (B and E) and 10 °C/min (C and F).

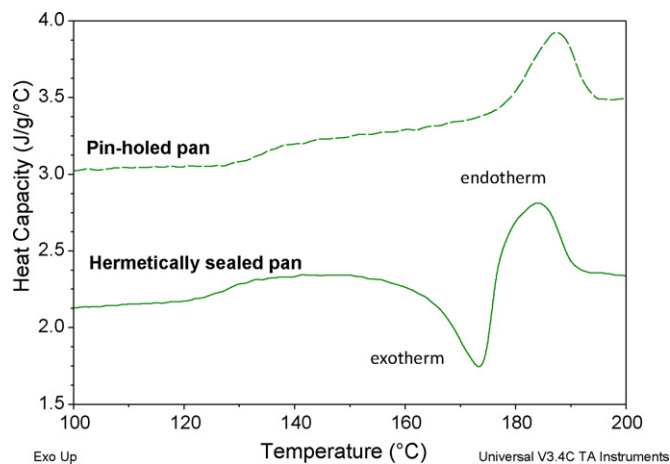


Fig. 3. DSC curves showing the response of EC sealed under ambient conditions in pin-holed pans (---) and hermetic pans (—), heated at 5 °C/min (data expressed as heat capacity).

and Tipper, 1978; Dubernet et al., 1990; Li et al., 1999), with McBurney (1949) suggesting peroxide formation as being the primary reaction mechanism. More specifically, the backbone of EC contains labile hydrogen atoms, which have shown to undergo thermo-oxidative degradation due to the formation of peroxide in the ether groups (primary reaction), followed by their decomposition with the removal of the corresponding aldehydes, alcohols, alkylhydroperoxides and other products as a result of peroxide decomposition (secondary reactions).

The issue in the present study is the link between the suggested oxidation process and the DSC results. Dubernet et al. (1990) noted an exothermic event at *circa* 180 °C which they suggested could be ascribed to exothermic oxidative degradation when the samples were run in hermetically sealed pans, although these authors did not observe the combined endo/exothermic peak noted here. In this study we have therefore provided supportive evidence for the exotherm being associated with oxidative degradation. This was further supported by investigating the effect of pan sealing conditions on the observed thermal events. The sample was run in pin-holed pans whereby the oxygen could be reasonably assumed to have been driven out prior to the degradation temperature being reached. Fig. 3 shows that the exotherm is no longer observed, a result consistent with the hypothesis of trapped air being responsible for the exotherm. Note that the exotherm appears at a lower temperature than was seen for the higher rate of 10 °C/min (Fig. 1), again reflecting the kinetically hindered nature of this event.

The hypothesis was further investigated by sealing the hermetic pans under a nitrogen purge atmosphere in a glove box. Weighed pans, sample and crimper were carefully transferred into the glove box and nitrogen was flowed through the system for at least 20 min prior to sealing, thus removing all or the majority of the oxygen. The results obtained were similar to those with pin-holed pans (data not shown), thus again supporting the exotherm being due to oxidative degradation but also highlighting the importance of considering pan choice when interpreting DSC results.

3.3. Investigation into the high temperature endothermic process

In order to investigate the endothermic response the system was examined using modulated temperature methods in crimped pans (to prevent the oxidation effect from being further observed, as there would be no entrapped headspace). Fig. 4 shows a typical MTDSC profile of EC which has been obtained by running at 2 °C/min with a modulation of ± 0.212 °C over 40 s. The data shows the endothermic transition starting at *circa* 175 °C during

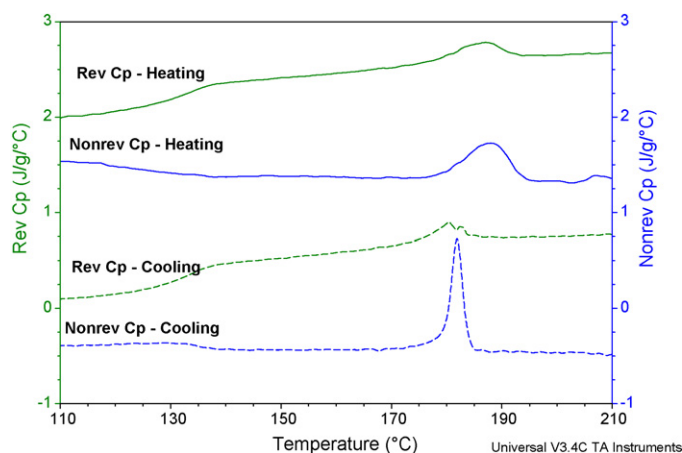


Fig. 4. Reversing and non-reversing heat capacity (C_p) signal of EC at $2^\circ\text{C}/\text{min}$ with a modulation of $\pm 0.212^\circ\text{C}$ over 40 s in crimped pans.

heating while a corresponding exotherm was detected over the same temperature range in the cooling signal, indicating temperature reversibility of the underlying process. Both responses showed components of reversing and non-reversing heat flow, indicating that these events contain both kinetic and reversing heat capacity components, although given the relatively narrow temperature range over which these events occur it is perfectly possible that the system may not be in steady state (i.e. the response to the underlying heat flow change may swamp the response to the modulation). This is a commonly recognized problem and hence alternative modulated approaches were explored for investigating this event. In particular, quasi-isothermal MTDSC is a means by which the heating rate is effectively negated via the holding of the sample at a range of selected temperatures about which the sample is modulated. Fig. 5 shows a typical Qi-MTDSC run of EC from room temperature to 220°C at modulation amplitude of $\pm 1^\circ\text{C}$ over 60 s (5 min isothermal time and 0.5°C temperature increment). The Qi-MTDSC plot fits the reversing heat capacity plot very well, including the uneven baseline and the T_g region. Significantly, in the endothermic region the majority of the excess reversing heat capacity deviation from the baseline (corresponding to the transition) was eliminated, although a small peak is still apparent. This will be discussed in more detail below.

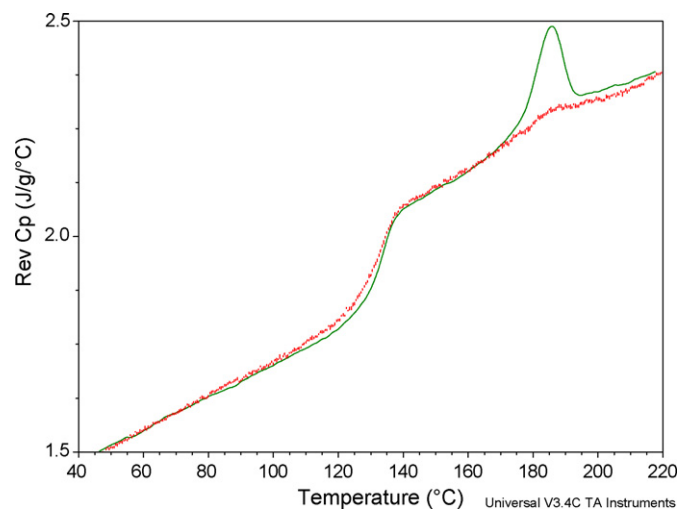


Fig. 5. Quasi-isothermal MTDSC (Qi-MTDSC) scan from room temperature to 220°C with 0.5°C temperature increment and 5 min isothermal time and ($\pm 1^\circ\text{C}$, 60 s) (discontinuous line) compared to corresponding MTDSC reversing heat flow signal (continuous line).

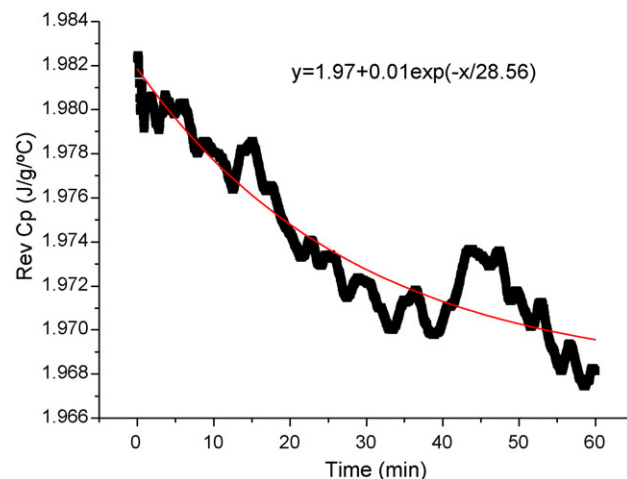
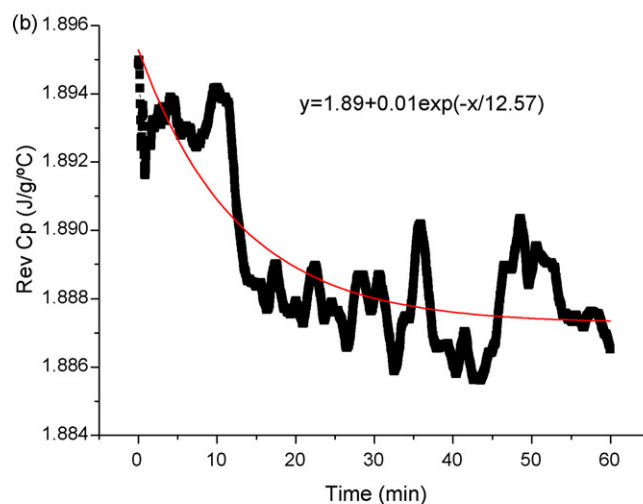
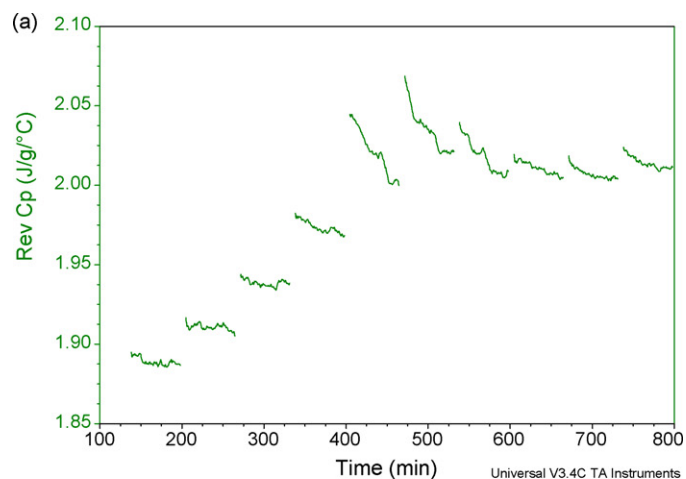


Fig. 6. (a) The plot of $\text{Rev } C_p$ against time of a typical quasi-isothermal MTDSC (Qi-MTDSC) of EC (1 h isothermal); temperatures (from left to right correspond to 160 to 205°C in 5°C increments). (b) Quasi-isothermal MTDSC curves for EC as a function of time at (top) 160°C and (bottom) 185°C , showing a first order exponential fit.

The quasi-isothermal method allows not only the equilibrium (or at least close to equilibrium) state of the system as a function of temperature to be observed but also facilitates observation of the process by which that equilibrium is reached. Fig. 6a shows the heat capacity as a function of time for hour-long isothermal periods at a series of temperature increments; one can clearly see the temperature range at which the heat capacity alters significantly through the transition, indicating a kinetic component to the event. Fig. 6b

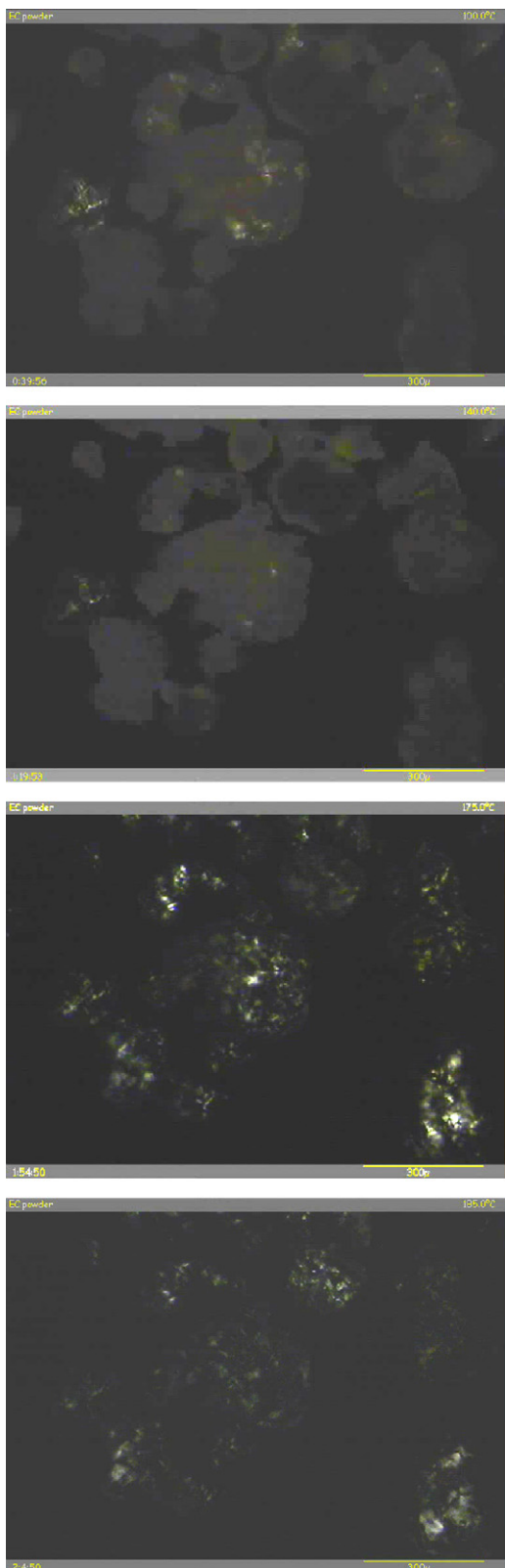


Fig. 7. Hot stage microscopy images (polarising light) of EC taken at 100, 140, 175 and 185 °C (top to bottom).

illustrates this effect for indicative temperatures of 160 and 185 °C. These plots were fitted to a first order exponential decay and the corresponding equations were displayed in each figure. However, given the uncertainties associated with the underlying process it was not considered appropriate to take such an analysis further

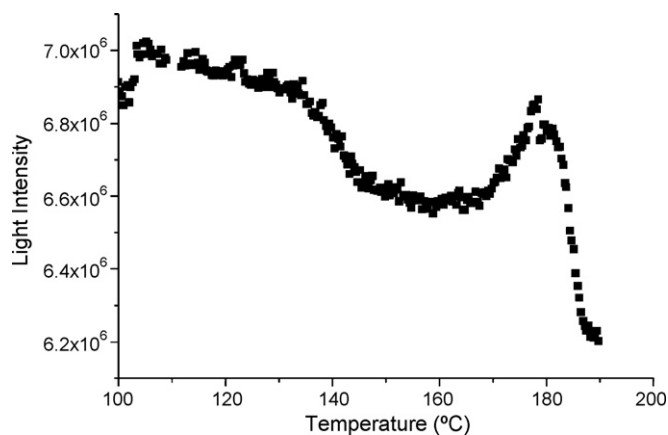


Fig. 8. Transmitted light intensity as a function of temperature observed under HSM during the heating of EC at 1 °C/min.

at this stage other than to note that the kinetics may indeed be monitored if not yet analysed with confidence.

When EC was visualized via HSM in cross-polar mode, a small degree of birefringence was observed at room temperature, indicating a degree of ordering within the system. Upon heating from room temperature to 200 °C at 1 °C/min, the initial birefringence disappears gradually up until *circa* 140 °C whereby a dark field was seen (Fig. 7). After this temperature, birefringence reappeared very rapidly and was more pronounced than before the heating program started. The peak of birefringence occurred at 175–180 °C but after this temperature decreased dramatically until 190 °C when the polymer fully liquefied. The light intensity versus temperature plot (Fig. 8) gives an indication of the transmission changes as the temperature increased. Perhaps surprisingly, this plot corresponds very well to the DSC curve shown in Fig. 1 in that light intensity discontinuities are seen at temperatures that correspond to both the T_g and endo/exotherm events. When the sample was cooled down at the same rate from 190 °C, birefringence reappeared at 170 °C and a similar pattern to that seen on the heating cycle was seen on further cooling to below T_g .

4. Discussion

The study has highlighted the thermal events associated with ethyl cellulose, with a particular view to developing new approaches to characterising the mechanisms underpinning these events. The T_g is in itself relatively straightforward, albeit relatively subtle, in turn indicating a strong glass former whereby the heat capacity change through T_g is limited. The baseline curvature noted was found to be a real effect and may be related to the changes in birefringence noted using the HSM; this is discussed in more detail below.

The events associated with the higher temperature endo/exotherm have been less extensively explored and were the main focus of study in this investigation. Again, the exotherm is reasonably straightforward in that there is compelling evidence from this and previous studies for this event being associated with oxidation. It is, however, particularly noteworthy that even the oxygen sealed into the hermetic pan as headspace can cause this effect and emphasises the need to carefully consider the choice of pans when performing DSC experiments. The endotherm was more difficult to characterise in a mechanistic sense, although the quasi-isothermal approach afforded valuable insights in this regard. In a series of thorough studies, the group of Wunderlich (Okazaki and Wunderlich, 1997; Wunderlich et al., 1999; Androsch and Wunderlich, 2000; Wunderlich, 2003) has discussed the significance of the quasi-isothermal response through endothermic

events. MTDSC techniques allow the thermal signal to be deconvoluted into reversing and non-reversing components according to

$$\frac{dQ}{dt} = C_p \cdot \frac{dT}{dt} + f(t, T) \quad (1)$$

where dQ/dt is the power output, C_p is the heat capacity, T and t the temperature and time respectively and $f(t, T)$ a kinetic component of the power response that is a function of time and temperature. In conventional scanning mode, the reversing component indicates the response to the superimposed modulation (a sine wave in the study used here) and, assuming steady state, reflects the underlying heat capacity component of the sample as a function of temperature. The sample temperature $T_S(t)$ may be given by

$$T_S(t) = T_0 + \langle q \rangle t - \langle q \rangle \frac{C_S}{K} + A \sin(\omega t - \varepsilon) \quad (2)$$

where T_0 is the initial temperature, $\langle q \rangle$ is the underlying heating rate, C_S is the heat capacity of the sample and pan, K is Newton's constant for temperature differential heat flux, A is the maximum amplitude, ω is the angular modulation frequency and ε is the phase shift relative to the temperature oscillation of the heater block. For quasi-isothermal studies, the instrument is set at a range of initial temperatures (T_0) with no underlying heating rate ($\langle q \rangle = 0$). The method allows the operator to establish the equilibrium (or close to equilibrium) value of heat capacity at any particular temperature by simply holding the sample for a sufficient time period so as to allow kinetic events to run to completion. Alternatively, the method allows the operator to monitor kinetic events by observing the change in heat capacity as a function of time. Both approaches have been used here.

In terms of the findings outlined here, there is a clear kinetic component to the endothermic response (Fig. 6) which predates away from a simple melting process such as one would observe for a highly crystalline, low molecular weight sample whereby melting would be expected to be effectively instantaneous. However, the quasi-isothermal responses as a function of temperature (Fig. 5) reveal that there is little apparent excess reversing heat capacity through the transition after modulation. In other words, the heat capacity peak seen for the MTDSC run represents the latent heat of the endothermic process rather than a change in the equilibrium heat capacity of the system as it is heated through the temperature range in question. This enables us to eliminate some possible mechanisms for the endotherm. The system shows little evidence for a reversible melting process such as may be found for some polymers such as poly(ethylene terephthalate) (Wunderlich et al., 1999), these effects being associated with nanoscale reorganisation during the melt. Similarly, the absence of an apparent excess reversing component may predicate against the system showing liquid crystalline behaviour as it has been noted that the transition may manifest as a significant reversible peak through the event, even when using quasi-isothermal mode, due to the isotropization of these systems being an essentially reversible reaction. Indeed, Wunderlich et al. (1999) have suggested that the DSC, MTDSC and quasi-isothermal responses may become identical for such materials.

Taking the above with the microscopy data, it is reasonable to suggest the presence of microcrystals within an otherwise amorphous matrix. The presence of such microcrystals within amorphous polymers has been discussed by Campbell (2000) and may represent unsubstituted regions of the cellulose backbone forming a condensed phase on an extremely small scale. The endothermic response (and exothermic event on cooling) may thus be ascribed to melting and crystallisation of these crystals, with the time dependence of the melting event seen with the Qi-MTDSC being a function of the high viscosity of the surrounding medium which lends a kinetic hindrance to the lattice dissipation process.

This is supported by HSM results which indicated a reduction in birefringence on holding the system at temperature through the endotherm (data not shown). It is also reasonable to suggest that the association process whereby these microcrystals are formed is enhanced above T_g due to greater mobility of these segments in a manner analogous to cold crystallisation of amorphous materials on heating. It is not clear why the initial birefringence disappears on heating up to T_g , although a reasonable suggestion would be that at low temperatures there may be loose, weak association between the unsubstituted regions that are disrupted on heating beyond ambient temperatures; above T_g the 'cold' crystallisation takes place over a wide temperature range (as supported by the HSM) and then melting occurs over a narrow temperature range which is detected as a defined endotherm.

The question naturally arises as to the relevance of these higher temperature processes to typical usage of the polymer, given that processing is highly unlikely to take place at these temperatures. The tendency to oxidation is of course important in itself, particularly as the timescales over which the material may be held at elevated temperatures during processes such as hot melt extrusion may be extensive. Indeed, the data presented here has clearly indicated that the onset temperature of degradation is highly dependent on the time of exposure to those elevated temperatures, hence a slow extrusion process at what may appear to be mild temperatures may in fact be sufficient to cause oxidation. The melting phenomenon is of interest for two reasons. Firstly, as will be demonstrated in a later communication, the presence of this event may greatly complicate interpretation of thermal data, particularly for drug loaded systems whereby the drug may melt over a very similar temperature range. Secondly, it is not clear whether the presence of these microcrystals may influence the mechanical and related properties of the material, particularly in the context of the use of ethylcellulose as a film coating material. Further study is ongoing to this effect.

A further aspect of the study has been the development of new approaches to the characterisation of this polymer. While MTDSC is now an industry standard, Qi-MTDSC has not been extensively used and has had little application within the pharmaceutical sciences. This study indicates that the method may have a range of applications including both kinetic and mechanistic studies. We also report the use of temperature scanning light intensity measurements. It is interesting to note that the method was able to identify a transition corresponding to T_g ; whether this is a direct correlation or is an indirect function of the increased fluidity of the sample after T_g is not yet clear, but it nevertheless represents an interesting new approach to study these systems.

5. Conclusions

The study has examined the thermal events associated with ethylcellulose and has indicated that the behaviour of this supposedly simple amorphous system may be much more complex than is commonly thought. In the first instance, the relatively subtle T_g may be measured using both conventional and modulated DSC, although the associated baseline drift renders assessment more difficult. However, at higher temperatures, the sample may undergo oxidative degradation (depending on the choice of pan and sealing environment) and an endothermic response that we ascribe to melting of microcrystals. This process may be usefully observed using Qi-MTDSC and appears to take place over a protracted period of over an hour; we suggest that this reflects the highly viscous nature of the surrounding medium. Overall therefore we present evidence for the structure of EC to be relatively complex, with the presence of microcrystals a distinct possibility. We also suggest that Qi-MTDSC and light intensity measurements represent an underused yet interesting approach to study these complex transitions.

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