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Effect of polymer molecular weight on the structural properties of non aqueous ethyl cellulose gels intended for topical drug delivery

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ABSTRACT

The structural properties of five ethyl cellulose polymers (EC) in mixture with the non aqueous solvent of propylene glycol dicaprylate (PGD) have been investigated with a view to facilitating topical drug delivery. Total concentration of the polymer varied from 12 to 20% (w/w) and its weight average molecular weight was in the range of 64–223 kDa. Experimental techniques utilised were small-deformation dynamic oscillation in shear, attenuated total reflectance Fourier transform infrared spectroscopy (ATR FTIR) and wide-angle X-ray diffraction. The nature of the time and temperature dependence on viscoelastic functions of all samples could be treated with the Chambon and Winter criterion allowing determination of the critical gelation temperature in relation to polymer concentration and molecular weight. A further refinement of this school of thought allowed correlation between the viscoelastic relaxation exponent and fractal dimensions in thermally treated EC/PGD matrices. Tangible evidence on the packing arrangements of the ethyl cellulose network and the molecular nature of its interaction with the non aqueous solvent as a function of polymer concentration and molecular weight was provided by X-ray diffraction and infrared studies.

1. Introduction

The polymer based semi-solid gel has been one of the most popular means of topical drug delivery. Hydrogels in particular have been widely utilised in the medical and pharmaceutical fields for their biocompatibility and similarity to natural tissue. Despite these widespread applications, they fail to be a suitable delivery system for moisture sensitive drugs, since the presence of water in the delivery vehicle affects the stability of chemical compounds included in formulations (Bonacucina, Cespi, Misici-Falzi, & Palmieri, 2006; Chow, Chan, & Heng, 2008). Previous results of this group demonstrated that a non aqueous preparation comprising ethyl cellulose (EC) and a non volatile solvent, propylene glycol dicaprylate (PGD), can be a promising topical drug delivery system because of its ability to form a structured gel network with satisfactory mechanical properties and textural consistency (Heng, Chan, & Chow, 2005).

The gelling mechanism of this EC/PGD system with respect to time and temperature of processing or application was also studied. Results argue that in contrast to thermoreversible gelation upon heating of aqueous ethyl cellulose solutions reported widely in the literature, replacing water with propylene glycol dicaprylate and mixing with the polymer yields gels that revert to the solution state with increasing temperature (Bruno, Kasapis, Chaudhary Chow, Heng, & Leong, 2011; Sun et al., 2009). This was rationalized by probing the specific polymer–solvent interactions as a function of experimental treatment. The effect of moisture was also studied, since the EC/PGD system is expected to come in contact with moisture during storage, production and application on the skin (Bruno, Kasapis & Heng, in press). Results throw light on the structural stability of preparations in the presence of moisture, the thermodynamic state of added water molecules at subzero temperature, as well as the specific interactions that take place between polymer, non aqueous solvent and aqueous phase in the composite gel.

Another attribute that affects the structural properties of the gel and ultimately its utility as a topical drug delivery system is the molecular weight of the polymer. There is scant information in the literature on this subject for cellulose derivatives. An attempt has been made to deal with the influence of polymer molecular weight on the properties of oleogels, intended for use as a lubricant grease, which were formulated with castor oil and ethyl cellulose or ethyl/methyl cellulose blends. The small-deformation mechanical behaviour of the latter preparation was enhanced by increasing ethyl-cellulose molecular weight and remained unaffected by temperature or timescale of observation (Sanchez, Franco, Delgado, Valencia, & Gallegos, 2011). The effect of ethyl cellulose on the

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stabilization of sucrose particles dispersed in vegetable fat was investigated with rheological techniques that examined in particular the attributes of polymer molecular weight and concentration. It was reported that fluidization of the sucrose/fat suspension in the presence of lecithin was little affected by the range of molecular weights utilised in that study (Do, Mitchell, Wolf, & Vieira, 2010).

In light of the above, this work is concerned with the effect of molecular weight of ethyl cellulose on the thermal and gelation properties of non aqueous gels. It utilises an appropriate school of thought to discuss the viscoelasticity, gel point and structural morphology of networks as a function of polymer concentration and molecular weight.

2. Materials and methods

2.1. Materials

The industrial ethyl cellulose samples of distinct molecular weights used in this study were water-insoluble, thermoplastic cellulose ethers with a randomly substituted pattern and a white powder appearance. The supplier provided data of the ethoxy content of the polymers and degree of substitution (d.s.), which are 49.0 ± 0.5% and about 2.6, respectively (Dow Chemical, Midland, MI). Weight average molecular weights (M_w) were obtained by gel permeation chromatography using Styragel column and a reflective index detector (Models 2690, 2410, Waters, Milford, MA) at 40 °C. Tetrahydrofuran was the mobile phase and polystyrene standards provided the calibration curve. Results expressed as means from duplicated determinations, which are close to supplier's information, are as follows: EC7 Ethocel std 7 FP Premium – 63,800; EC10 Ethocel std 10 FP Premium; 79,200; EC20 Ethocel Std 20 Premium – 124,400; EC45 Ethocel Std 45 Premium – 159,900; EC100 Ethocel Std 100 FP Premium – 223,200.

The non-aqueous solvent used presently is a hydrophobic diester derivative of propylene glycol and it is commercially available by Sasol GmbH, Witten, Germany. The solvent is a non-volatile neutral oil exhibiting viscosity of about 10 MPa s at 20 °C with caprylic acid and capric acid contents of 65–80% and 20–35%, respectively (propylene glycol dicaprylate/dicaprate (PGD); Miglyol 840).

2.2. Gel preparation

Gels of variable concentration (12–20%, w/w) and molecular weight of ethyl cellulose were prepared by mixing the polymer with propylene glycol dicaprylate/dicaprate using continuous stirring with a magnetic stirrer at 300 rpm at ambient temperature for 15 min. That led to the formation of a homogeneous material following air-bubble removal by applying vacuum. All material concentrations are expressed in this work on a weight-per-weight basis.

2.3. Rheological measurements

Small deformation dynamic-oscillation measurements in shear were performed using AR-G2, a rheometer with a magnetic thrust bearing technology for nano-torque control (TA Instruments, New Castle, DE). The analysis provides readings of the storage modulus (G'), which is the elastic component of the network, loss modulus (G''; viscous component) and complex dynamic viscosity (η^*). Variations with time and temperature can further be assessed as a measure of the 'phase lag' δ ($\tan \delta = G''/G'$) of the relative liquid-like and solid-like structure of the material. Temperature control is achieved with a Peltier plate at a range between −30 and 120 °C and accuracy of ±0.1 °C. Experimental routines were carried out within the linear viscoelastic region (LVR) of the material, loaded onto the parallel plates of the measuring geometry (40 mm diameter; 2 mm gap).

Frequency sweeps of unheated and heated EC/PGD gels was carried out at 25 °C between 0.1 and 100 rad/s using 0.5% strain. Controlled heating and cooling of these gels at a scan rate of 1 °C/min was within the temperature range of 25–90 °C at a frequency of 1 rad/s and 0.5% strain. Finally, thermal routines for the estimation of $\tan \delta$ as a function of temperature in Fig. 3 extended the work to frequencies of 0.5, 1.5 and 2 rad/s at the same scan rate and applied strain. Five ethyl cellulose variants were investigated and in each case three samples were prepared and tested separately. Averages of essentially overlapping traces of shear modulus are reported for every variant leading to consistent results as a function of polymer concentration and molecular weight for the critical gelation temperature, viscoelastic relaxation exponent and fractal dimension.

2.4. ATR-FTIR analysis

ATR-FTIR spectra of the EC/PGD samples were obtained using a Perkin Elmer One^{TM} FTIR spectrometer equipped with MIRacle^{TM} ZnSe single reflection ATR plate (Perkin-Elmer, Norwalk, CT). The spectrum of each material was finalized after averaging 200 scans between 4000 and 600 cm^{-1} with a resolution of 4 cm^{-1}. This was corrected against the background spectrum of the solvent at ambient temperature. Data acquisition was facilitated by the Spectrum v5.0.1 Software of Perkin-Elmer.

2.5. X-ray diffraction studies

Wide-angle X-ray diffraction patterns of the EC/PGD samples were obtained using a SIEMENS D5005 X-Ray Diffractometer (Bruker AXS, Karlsruhe, Germany) equipped with Cu-Kα (1.54 Å) radiation. An accelerating voltage and current of 40 kV and 40 mA, respectively, in combination with a scan rate of 0.8 °C/min were employed. The diffractograms were recorded in a 2θ range between 2° and 90° in measuring intervals of 0.1°, and subsequently analysed using the Bruker Advanced X-Ray Solutions software, DIFFRAC^{plus} Evaluation (Eva), version 10.0 revision 1.

3. Results and discussion

3.1. Frequency dependence of viscoelasticity in non-aqueous EC gels varying in molecular weight

The frequency dependence of storage and loss modulus for freshly made gels of 12% EC/PGD with different molecular weights at 25 °C is shown in Fig. 1a. In the case of low molecular weight materials (EC7 and EC10), G'' values are higher than G' hence arguing for viscoelastic solutions in the original state of preparation. A transformation from a predominant liquid state to that of a weak physical gel (Chen, Liao, & Dunstan, 2002), exhibiting considerable frequency dependence with increasing polymer molecular weight is recorded for EC20 and EC45. The strongest gels are formed in EC100 samples, an outcome which is attributed to considerable increase in chain length, hence connectivity, at this grade of ethyl cellulose polymers.

There is a change in rheological profiles once systems are exposed to a thermal regime comprising heating up to 90 °C followed by cooling to 25 °C. As illustrated in Fig. 1b, samples for all tested molecular weights of ethyl cellulose in propylene glycol dicaprylate form three dimensional structures with thermal treatment, with values of storage modulus largely predominating those of loss modulus. Gels are relatively weak in EC7 and EC10, and this is reflected in cross-over of modulus traces at the high frequency end of the spectrum ($G'' > G'$). Increasing molecular

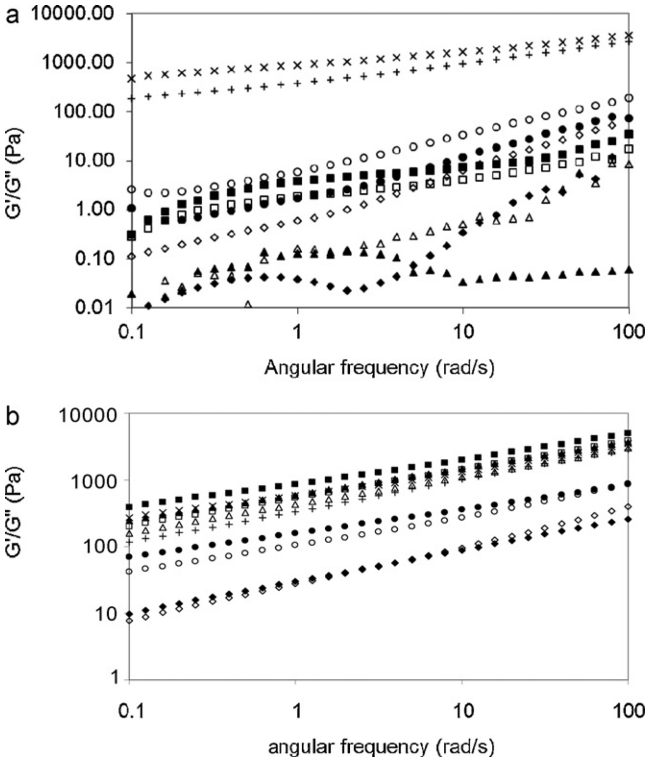

Fig. 1. Frequency variation of storage modulus (closed symbols) and loss modulus (open symbols) of (a) unheated and (b) heated 12% EC/PGD gels in relation to polymer molecular weight: EC7 (♦;◊), EC10 (●;○), EC20 (▲;△), EC45 (■;□), and EC100 (X;+).

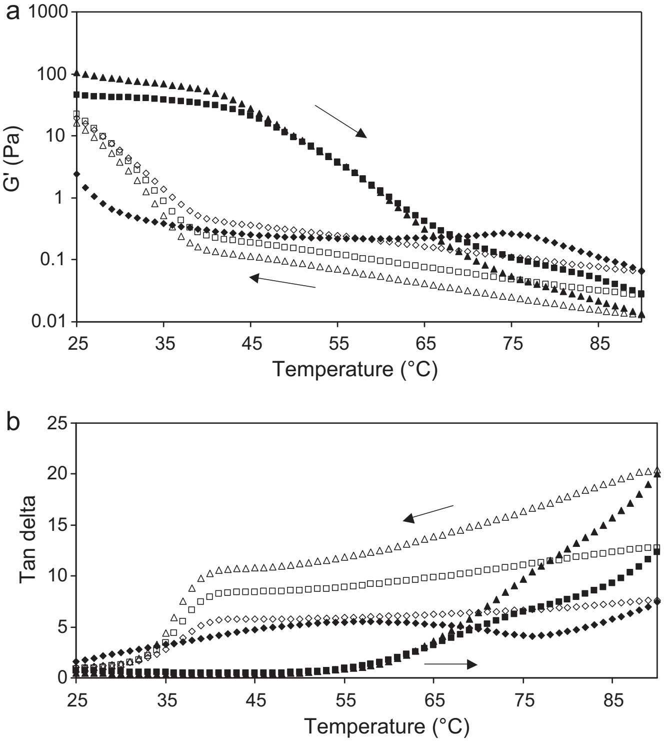

Fig. 2. Storage modulus (a) and tan δ (b) obtained from controlled heating (closed symbols) and cooling (open symbols) at 1 °C/min for the 12% EC7/PGD gel: first temperature sweep (♦;◊), second temperature sweep following isothermal ageing at 25 °C for 48 h (■;□), and third temperature sweep (▲;△) following another isothermal ageing period at 25 °C for 48 h (frequency: 1 rad/s; strain: 0.5%).

weight produces networks of the order of 10^3 Pa throughout the experimentally available frequency range (0.1–100 rad/s), which indicates that these systems (for example, EC45 and EC100) may constitute appropriate media for topical skin treatment and drug delivery.

3.2. Viscoelastic profiles of EC/PGD systems over a wide temperature range

In order to delve into the nature of the molecular forces that govern the transformation recorded in the frequency sweeps of Fig. 1a and b with thermal treatment, samples were subjected to an experimental routine that involved three controlled heating and cooling routines at 1 °C/min separated by two isothermal runs of 48 h each. Results are depicted in Fig. 2a and b for the storage modulus and tan δ of 12% EC7/PGD preparations but, qualitatively, similar responses were obtained for the remaining four counterparts (data are not shown here).

Clearly, the first thermal profile was appreciably different from the rest by lacking thermal hysteresis and exhibiting higher values of G' at the end of the cooling run, as compared to the start of the experimental routine (heating). The second (and third) thermal profile of the system requires a 48 h isothermal run between the heating and cooling runs for complete recovery of the storage modulus. This temperature effect argues for direct interactions between polymer and solvent to yield specific viscoelastic profiles.

On the basis of regioselectively substituted hydroxyl groups with benzyl, methyl and ethyl ether, it can been argued that the drop in the values of storage modulus that continues unabated up to 65 °C in Fig. 2a is associated with direct polymer–polymer hydrogen bonding featuring 6-position hydroxyl groups (Itagaki, Tokai, & Kondo, 1997; Kondo & Miyamoto, 1998). The second wave of structure formation observed at temperatures below 40 °C in tan δ traces in Fig. 2b may involve an additional contribution from electrostatic interactions between carbonyl groups of the solvent and hydroxyl groups of the polymer. This has been argued for EC gels using diethyl, dibutyl and di(2-ethylhexyl) phalate solvents, which produced networks with a flat frequency dependence of shear modulus on dynamic oscillation due to the formation of stable bridges between the two carbonyl groups of each diester-phalate molecule and two encompassing EC chains (Lizaso, Munoz, & Santamaria, 1999). Our results in Fig. 1b show a pronounced frequency dependence of shear modulus attributed to freely rotating single bonds of the dicaprylate/dicaprate backbone that reduce the efficiency of carbonyl-group polarization in EC/PGD gels. Since this is a universal theme in the gels of EC7, EC10, EC20, EC45 and EC100 tested presently, it is suggested that a change in the degree of substitution can affect the two rheological transitions observed, as opposed to molecular weight considerations.

3.3. Determination of the critical gelation temperature for EC/PGD preparations in relation to polymer concentration and molecular weight

A critical consideration in discussing the structural properties of a polymeric matrix is the identification of its sol–gel transition. Conventionally, this is given as the crossover of storage and loss modulus traces as a function of temperature or timescale of observation (Ferry, 1980). In most of the synthetic and biological gels, however, the gelation temperature identified by this method is found to be frequency dependent (Winter, Izuka, & De Rosa, 1994), which diminishes the physical significance of such prediction. In order to determine the critical gelation temperature (T_{gel}) for the EC/PGD sample as a function of polymer concentration and molecular weight, we utilised a fundamental approach proposed by Chambon and Winter (1985, 1987). According to this, the value

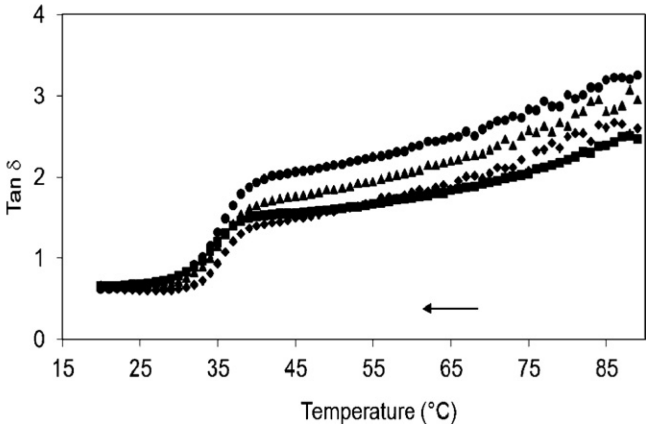

Fig. 3. Values of tan δ as a function of temperature for the 12% EC10/PGD gel scanned at different experimental frequencies: 0.5 rad/s (◆), 1 rad/s (▲), 1.5 rad/s (●), and 2 rad/s (■).

of T_{gel} is determined by recording multi frequency plots of tan δ versus experimental temperature or time. This generates a frequency independent value of tan δ that can be expressed as follows:

$$tan\,\delta = \frac{G''}{G'} = \tan\left(\frac{n\pi}{2}\right) \qquad (1)$$

where n is the critical exponent that becomes a parameter of the material and is physically restricted to $0 < n < 1$. The phase angle between stress and strain, δ, is thus independent of frequency but proportional to this relaxation exponent.

This criterion was initially developed for chemical (synthetic) networks but, subsequently, was extended to physical (biological) gels (Cuvelier, Peigney-Nourry, & Launay, 1990; Te Nijenhuis & Winter, 1989). Fig. 3 reproduces the multi frequency plot (0.5, 1, 1.5 and 2 rad/s) of tan δ with temperature for 12% EC10/PGD gels but a similar qualitative response was monitored for all ethyl cellulose samples (data are not shown here). Curves pass through a common point at a certain temperature, which is defined as the gel point or critical gelation temperature, and the procedure was repeated for various polymer concentrations and molecular weights, with results being summarized in Table 1. In general, T_{gel} values were comparable among all concentrations at any given polymeric preparation. However, higher molecular weights, in particular those of EC45 and EC100, lead to elevated gelation temperatures, an outcome that should be attributed to an increase in the collision probability of polymer chains thereby facilitating early network formation. Further, T_{gel} predictions in Table 1 appear to be lower than the temperature of 40 °C below which in Fig. 2b values of tan δ fall sharply during the standard cooling routine of this investigation. The latter, therefore, reflects a non equilibrium pseudo state and further cooling is required for vestigial formation of a continuous three-dimensional structure in EC/PGD systems.

Following successful application of the Chambon and Winter criterion in this study, we obtained frequency sweeps for thermally treated samples at the predicted critical gelation temperatures. Work was carried out for all concentrations in Table 1 and available molecular weights, with Fig. 4 depicting a typical frequency sweep of 12% EC10/PGD at T_{gel} (i.e. 22 °C). At the gel point, G' and G'' traces exhibit a power law behaviour with a dominant solid-like viscoelasticity over an extended frequency range, whose mathematical expression is given below:

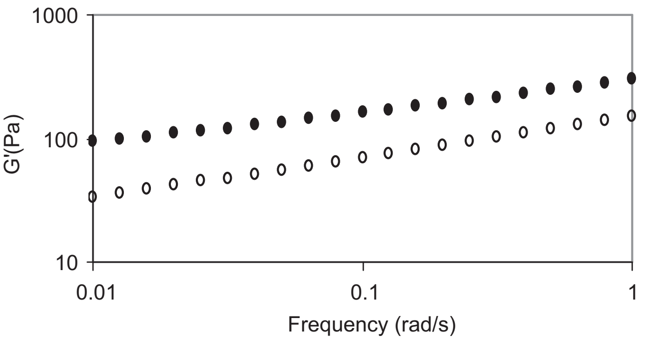

Fig. 4. Power law dependence of G' (●) and G'' (○) with frequency of oscillation obtained at the critical gelation temperature (T_{gel} = 22 °C) of the 12% EC10/PGD gel.

$$G'(\omega) \approx G''(\omega) \propto \omega^{n} (0 < n < 1) \qquad (2)$$

where ω is the angular frequency of oscillation and n is the critical or scaling exponent, which takes up the same physical meaning as for the corresponding material parameter in Eq. (1).

3.4. Derivation of the relaxation exponent and fractal dimension in thermally treated EC/PGD gels

We have combined Eqs. (1) and (2) so that experimental observations from frequency sweeps can be treated with a school of thought that provides fundamental information on the relaxation exponent of our systems. According to the literature, stiff materials at the critical gel point have a small n value ($0 \leftarrow n < 0.5$), whereas soft and fragile materials have a large n value ($0.5 < n \rightarrow 1$) (Tan, Pan, & Pan, 2008). Values reported are for gelatin hydrogels, $n = 0.69$ (Hsu & Jamieson, 1993), calcium pectate, $n = 0.72$ (Axelos & Kolb, 1990), physically cross linked PVC/plastisol, $n = 0.8$ (Te Nijenhuis & Winter, 1989), physically crystallizing polypropylene, $n = 0.2$ (Lin, Mallin, Chien, & Winter, 1991) and lentinan physical gels, $n = 0.4$ (Zhang, Xu, Xu, & Zhang, 2007).

Fig. 5 reproduces values of the viscoelastic relaxation exponent, which for all polymeric concentrations and molecular weights were found to be within the range of 0.41 ± 0.03. Increase in cross linking density can cause a decrease in n values (Li & Aoki, 1998), hence the slightly lower predictions at high concentrations of ethyl cellulose (20%) may be the outcome of dense physical interactions in this matrix. Values of the relaxation exponent argue for relatively stiff gels supported by the high intrinsic persistence length of the ethyl cellulose chain, which is in the order of 10 nm (Hoogendam et al., 1998), and polymer–polymer hydrogen bonding with carbonyl–hydroxyl group polarization according to our earlier discussion. Similarly, the low value of $n = 0.2$ for physically crystallizing polypropylene is due to associations having a long lifetime

Table 1
Critical gelation temperature of EC/PGD gels as a function of polymer concentration and molecular weight.

Polymer concentration (w/w%)	EC7 T_{gel} (°C)	EC10 T_{gel} (°C)	EC20 T_{gel} (°C)	EC45 T_{gel} (°C)	EC100 T_{gel} (°C)
12	20	22	21	25	25
14	20	18	19	21	24
16	20	18	17	23	23
18	18	17	18	25	28
20	19	19	20	24	30

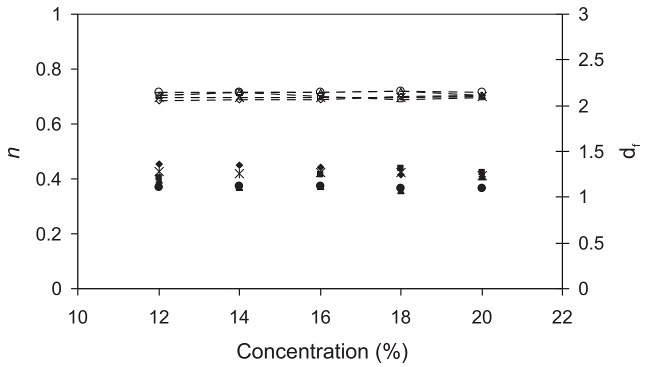

Fig. 5. Effect of polymer concentration on the viscoelastic relaxation exponent, *n* (closed symbols) and fractal dimension, d_f (open symbols) for gels with different polymer molecular weight: EC7/PGD (*;X), EC10/PGD (●;○), EC20/PGD (▲;△), EC45/PGD (■;□), and EC100/PGD (⧫;◊).

that is comparable to chemical crosslinks, and the value of $n = 0.4$ for lentinan is due to an entangled triple helix forming a stiff network.

A further refinement of this discussion refers to a model that establishes the relationship between viscoelastic relaxation exponent and fractal morphology of the gel network (Muthukumar, 1989). Building on this idea, the structure of a network at the gel point is represented by a fractal dimension, d_f, which is defined as $R^{df} \approx M$, where *R* is the radius of gyration and *M* is the mass of a molecular cluster. If the excluded volume effect is fully screened (details of the theory in the above reference), the relationship between *n* and d_f can be expressed as follows:

$$n = \frac{d(d+2-2d_f)}{2(d+2-d_f)} \qquad (3)$$

where $d = 3$ is the spatial dimension. Based on this equation, all values of the relaxation exponent $0 < n < 1$ are possible for a fractal in the physically realisable domain $1 \leq d_f \geq 3$.

In using Eq. (3), we expect that in the dense concentration regime of our systems, i.e. 12–20% (w/w) polymer concentration, the well known screening of the excluded-volume effect will take place (Muthukumar, 1985). Such shrinkage of the size of the polymer or “draining” of its hydrodynamic volume occurs especially at conditions of the gel point, as for the present investigation. Application of this approach to the viscoelasticity of our gels with variable polymer concentration and molecular weight near their gel points generates values of fractal dimension also shown in Fig. 5. These represent the compactness of particles within a cluster and high estimates indicate the formation of a rather compact network structure (Nystrom, Walderhaug, & Hansen, 1995; Shen, Wan, & Gao, 2010). Regardless of polymer concentration and molecular weight, d_f values of just above 2.0 were obtained, which further support the predictions of the relaxation exponent for a relatively stiff, homogeneous and compact EC/PGD gel.

3.5. *X-ray diffraction studies of ethyl cellulose powders and in the presence of a non-aqueous solvent*

Besides the theoretical treatment of rheological results dealt with in the preceding sections, we felt that XRD patterns would provide tangible evidence of the effect of polymer molecular weight on its packing arrangement in these systems. Polymer chains consisting of alternating sequences of rigid and flexible units may exhibit liquid crystallinity if the rigid sequences are sufficiently long as in the case of cellulose and its derivatives. In here the dominant source of flexibility arises from pseudo rotation of an occasional sugar ring, causing the O—C and C—O bonds pendant to the aberrant ring to adopt transverse directions (Flory, 1984).

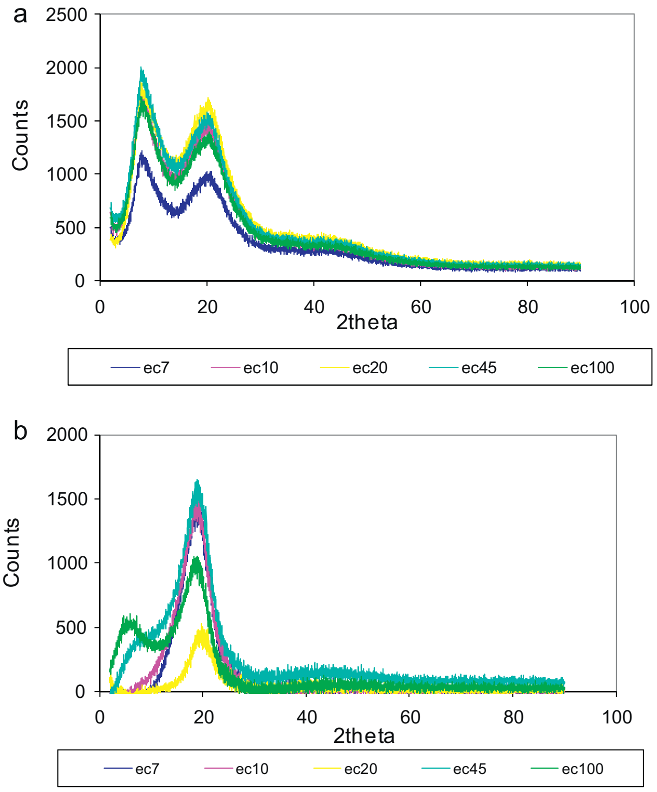

Fig. 6. Wide-angle X-ray diffraction patterns for (a) ethyl cellulose powders of different polymer molecular weight and (b) freshly made 12% EC/PGD gels of different polymer molecular weight.

As seen in Fig. 6a, the five EC powders with different molecular weights show two peaks around 2θ angles of 8.1 and 20.6, which are representative of liquid crystallinity (Huang, Ge, Li, & Hou, 2007). The former peak reflects the interlayer distance of ordered chains whereas the second peak corresponds to interchain distance. Considerable changes are noticed upon addition of solvent, with the freshly prepared gels of EC7, EC10 and EC20 in the presence of propylene glycol dicaprylate showing only a single peak at around 2θ angle of 20.2 (Fig. 6b). In the case of the EC45 gel, a barely developed second peak can be seen around 2θ angle of 7.1, whereas two fully developed peaks are clearly discernable for the EC100/PGD gel. Therefore, it appears that only the highest molecular weight material was able to maintain the liquid-crystal fingerprints in the non aqueous environment of the PGD solvent.

There has not been much work on the effect of polymer molecular weight on cholesteric liquid crystallinity of cellulose or its derivatives. Concentrated solutions of cellulose acetate in trifluoroacetic acid were found to form cholesteric liquid crystals and on the basis of circular dichroism spectra it was concluded, that under equivalent conditions of thermal treatment and polymer concentration, formation of ordered assemblies was a direct function of polymer molecular weight (Sixou, Lematre, Ten Bosch, Gilli, & Dayan, 1983). A second study dealing with changes in the pitch of a cholesteric liquid crystal also showed that solutions of high molecular weight polymer (derivative of cyclohexanedicarboxylate) were densely crystalline (Hara, Satoh, Toya, Iida, & Orii, 1988). Therefore, the literature offers an indication as to the ability of the ordered and long polymeric sequences of EC100 to partially resist disruption following solvent addition hence maintaining cholesteric liquid crystalline behaviour in the gels, notably in the form of the interlayer distance of ordered chains.

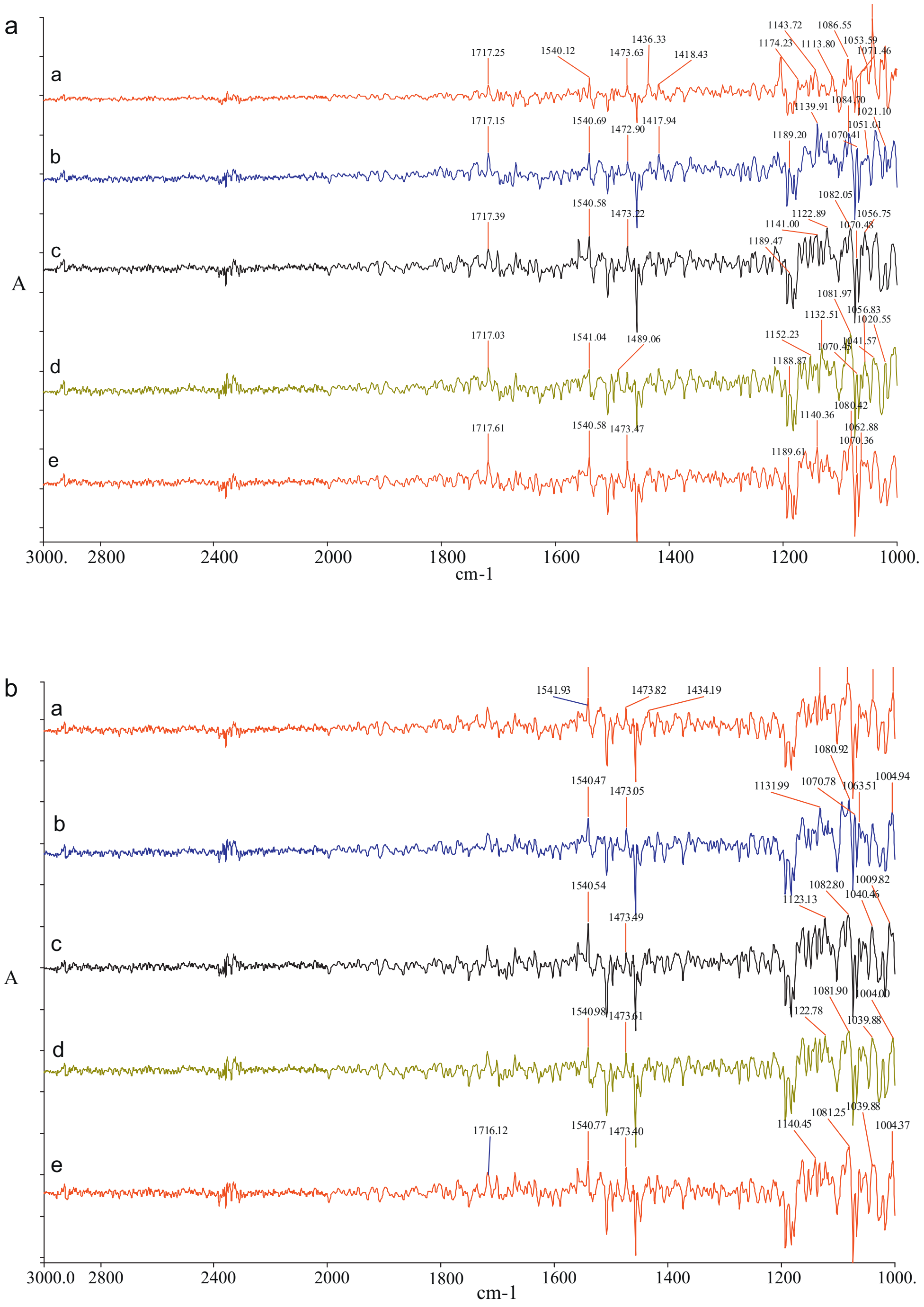

Fig. 7. ATR FTIR spectra of 12% EC/PGD with different polymer molecular weight: (a) EC7, (b) EC10, (c) EC20, (d) EC45, and (e) EC100, following thermal treatment (a) and for freshly made gels (b).

3.6. ATR FTIR studies of EC/PGD gels prior and following thermal treatment

Further information on the nature of interactions between polymer and solvent is provided by infrared studies and Fig. 7a illustrates the spectra for thermally treated gels. The focus of the current discussion is on the peak at 1717 cm^{-1}, which represents the ester carbonyl group of the non aqueous solvent. This absorbance is only faintly seen in the unheated gels (Fig. 7b), but is relatively strong being detected in their heated counterparts. The peak is indicative of interactions taking place between hydroxyl groups of the polymer and ester groups of the solvent. Thus the FTIR spectrum further confirms experimental observations from rheology and X-ray diffraction arguing for the utility of the thermal treatment in partially disturbing the packing arrangement of ethyl cellulose powders/untreated gels leading to direct interactions between polymer and solvent.

4. Conclusions

The present investigation develops a quantitative relationship between concentration or molecular weight and viscoelastic properties of ethyl cellulose in the presence of the non-aqueous solvent of propylene glycol dicaprylate. In contrast to thermoreversible gelation upon heating of aqueous ethyl cellulose solutions reported widely in the literature, replacing water with propylene glycol dicaprylate and mixing with the polymer yields gels at ambient temperature that revert to the solution state with increasing temperature. This is a universal theme in viscoelasticity regardless of polymer concentration and molecular weight. Network formation was rationalized by proposing specific polymer–polymer hydrogen bonding, which is further supported by additional contributions from electrostatic interactions between carbonyl groups of the solvent and hydroxyl groups of the polymer. Theoretical modeling argues that high molecular weight materials experience elevated gelation temperatures due to an increase in the probability of collision and effective association of polymer chains leading to infinite "subtree" linkages according to the network connectivity theory. Material parameters reflecting the viscoelastic relaxation exponent and fractal dimension of structured assemblies were also derived. These indicate that polymer concentration or molecular weight, within the experimentally available range, did not affect the structure of EC/PGD gels, which were found to form relatively stiff and compact networks. From an applications viewpoint in the pharmaceutical industry, identifying the fundamental structural characteristics of these systems ushers in an opportunity for innovation in topical drug delivery.

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