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Research Paper

Development of Novel Nonaqueous Ethylcellulose Gel Matrices: Rheological and Mechanical Characterization

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Purpose. This study reports the rheological and mechanical characterization of novel non-aqueous ethylcellulose gel matrices intended for topical drug delivery. An attempt was also made to explain the molecular interaction within the gel systems from a molecular conformational approach.
Methods. Nonaqueous gel matrices were prepared from three fine particle grades of ethylcellulose and propylene glycol dicaprylate/dicaprate. Continuous and oscillatory shear rheometry was performed using a cone-and-plate rheometer and mechanical characterization was performed using a universal tensile tester.
Results. The gel matrices exhibited prominent viscoelastic behaviour, yield stress and thixotropy. Rheological and mechanical properties showed significant upward trends with increased polymeric chain length and polymer concentrations. Good linear correlations were obtained between rheological and mechanical properties. The solvent molecular conformation was found to play a role in affecting the formation of gel networks via intermolecular hydrogen bonding between ethylcellulose polymer chains.
Conclusions. Ethylcellulose was successfully formulated as a nonaqueous gel with propylene glycol dicaprylate/dicaprate. The novel nonaqueous gel exhibited rheological profiles corresponding to a physically cross-linked three dimensional gel network, with suitable mechanical characteristics for use as a vehicle for topical drug delivery. Molecular conformation of the solvent was found to influence the molecular interactions associated with formation of ethylcellulose gel networks.

KEY WORDS: Ethylcellulose, nonaqueous gel, rheology, viscoelasticity, mechanical properties.

INTRODUCTION

Aqueous gels are much better studied than nonaqueous gels because hydrophilic gelling agents are readily available. However, the presence of water in aqueous gels may not be desirable when formulating moisture-sensitive drugs as chemical stability problem is almost inevitable when such drugs are incorporated into water-containing systems (1,2). The availability of a substantial number of topically useful but moisture-sensitive drugs in the market calls for the formulation of a suitable vehicle that can ensure drug stability. Improved stability has been reported for some hydroalcoholic gels (3), but the hydrophilic nature of these gels can still pose a risk of drug hydrolysis. In addition to the above, the use of ethanol in topical gels can potentially cause undesirable variation in formulation composition due to its high evaporative potential. Hence, it is important to develop a vehicle that does not contain water but possesses better or similar rheological and mechanical properties with hydrophilic gels in order to eliminate the possibility of drug hydrolysis. A nonaqueous hydrophobic gel will be suitable to address this problem. However, most polymers are not able to form gel in hydrophobic solvents.

Ethylcellulose (EC) is often used as a polymer for coating, as a matrix material in controlled-release oral dosage forms (4–6), as an excipient in topical or transdermal films (7) and patches (8), as well as a particulate emulsion stabilizer owing to its surface active property (9). The flexibility, hydrophobicity, and low water permeability of EC film allowed it to be an effective backing material for buccal delivery devices (10). Although EC is a popular polymer in film-forming applications, its use in the formulation of nonaqueous gels remains largely unexplored. EC gels prepared using solvents such as ethanol and diester phthalates have been reported (11–13). The former solvent has been successfully used in EC gels to achieve transdermal drug delivery (12,13), but it suffers the disadvantage of high volatility. Preparation using the latter solvents involved the use of high temperature of 180°C, which would entail great technical difficulties. In the current study, a novel nonaqueous EC gel formulation was developed using a nonvolatile solvent composed of a hydrophobic diester derivative of propylene glycol. The gel could be readily prepared using a slightly elevated temperature of 60°C.

A topical dosage form should satisfy some physicochemical and aesthetic criteria to ensure its clinical efficacy and patient acceptability. Desirable attributes cited for topical dosage forms include optimal rheological and mechanical properties (14), which are often associated with drug release kinetics, bioadhesion, and the ability of the dosage form to withstand mechanical stresses due to body movements. Rhe-

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ological and mechanical characterization is widely reported for aqueous gels of cellulose derivatives (15,16). Although the different aspects of rheological behavior of EC/*m*-cresol lyotropic liquid crystalline solutions have been extensively reported (17,18), there is only one study on the dynamic rheological property of nonaqueous EC gels (11). The limited information available on the rheological and mechanical properties of nonaqueous EC gels warrants more in-depth studies on such gel systems. This study reports the rheological and mechanical characterization of a novel nonaqueous EC gel intended for topical drug delivery. An attempt was made to explain the molecular interactions within the gel system based on the molecular structures of the polymer and solvent.

MATERIALS AND METHODS

Materials

EC polymers of increasing chain length with ethoxyl content of 48.0-49.5% [Ethocel Std 7 FP Premium (EC7), Ethocel Std 10 FP Premium (EC10), and Ethocel Std 100 FP Premium (EC100)] and propylene glycol dicaprylate/dicaprate (Miglyol 840) were gifts from Dow Chemical (Midland, MI, USA) and Sasol (Hamburg, Germany), respectively. Liquid paraffin was obtained from BDH (Poole, England).

Preparation of Gels

EC was dissolved in the nonaqueous solvent (Miglyol 840) with continuous stirring at 60°C to form a gel. For large volumes of gel samples, mixing was carried out with the aid of a ball mill (Retsch, Haan, Germany). Six formulations of different EC concentrations were prepared from each grade of the polymer: 11% to 16% w/w for EC7 and EC10, and 7% to 12% w/w for EC100. Trapped air bubbles were removed from the gel samples using vacuum. The gels were kept for 24 h to ensure complete swelling prior to any testing.

Rheological Measurements

Continuous and oscillatory shear rheometry was performed using a cone-and-plate rheometer (ThermoHaake RheoStress 1, Haake, Karlsruhe, Germany), with cone of 60-mm diameter and 1° cone angle at a controlled temperature of 25 ± 0.5°C (ThermoHaake Circulator DC30). The gel sample was carefully applied to the lower plate to minimize shearing effects and allowed to equilibrate for about 10 min prior to measurement. Each measurement was carried out using a fresh sample. At least three samples were measured for each formulation and the mean values of the various parameters reported.

Continuous Shear Rheometry

The upward and downward flow curves were measured in the controlled-rate mode by changing the shear rate from $0.001\ \mathrm{s}^{-1}$ to $60\ \mathrm{s}^{-1}$ over a period of 600 s. The upward flow curves were modeled using the Oswald-de-Waele equation (19):

$$\sigma = \mathrm{k}\gamma^{n}$$

where σ = shear stress, γ = shear rate, k = consistency index, and n = flow behavior index.

Estimation of yield stress was done by fitting the data on the upward flow curve to the Casson's model (19):

$$\sigma^{1/2} = {\sigma_y}^{1/2} + (\eta\gamma)^{1/2} \qquad \text{for } \sigma > \sigma_y$$

where σ_y = yield stress and η = shear viscosity (creep viscosity).

In order to validate the applicability of the rheometer and the Oswald-de-Waele model under the above experimental conditions, the experiment was repeated with liquid paraffin, which should give a rheogram typical of a Newtonian fluid.

Oscillatory Shear Rheometry

Oscillatory stress sweeps were performed at a constant angular frequency of $1\ \mathrm{rad\ s}^{-1}$ over a stress range of 0.1 to 500 Pa. Oscillatory frequency sweeps were carried out over a frequency range of 0.1 to $100\ \mathrm{rad\ s}^{-1}$ at a constant stress amplitude of 1 Pa where all the gel samples were within linear viscoelastic region as shown by the oscillatory stress sweep profiles. Viscoelastic parameters which included shear modulus (storage modulus, G' and loss modulus, G''), loss tangent ($\tan \delta$) and dynamic viscosity (η^*) were obtained.

Mechanical Characterization

Mechanical characterization of the gel samples were performed using a universal tensile machine with a 100 N load cell (EZ-Tester, Shimadzu Corporation, Japan) to obtain hardness, compressibility, cohesion and adhesiveness parameters. The experimental methods were adapted from those used by Jones *et al.* (20). Gel samples were filled into 50 ml beakers, to a fixed height of about 4.5 cm immediately after their preparation. The slightly elevated temperature of the freshly prepared gel resulted in a lower gel consistency that facilitated the flow of the gel into the beaker. Trapped air bubbles in the gel were then removed by vacuum and the gel stored for 24 h at room temperature of 22 ± 0.5°C before mechanical testing. The gel was compressed twice by the compression probe of 25 mm diameter to a depth of 15 mm at a rate of $10\ \mathrm{mm\ s}^{-1}$, with a recovery period of 60 s between the end of the first compression and the start of the second compression. At least three samples were measured for each formulation and the mean values of the various parameters reported. From the force-displacement plot, hardness was defined as the maximum load stress attained on gel compression whereas cohesion was defined as the minimum load stress on probe withdrawal from the gel. These parameters were measures of the resistance to penetration and to withdrawal of the probe. Compressibility was defined as the work required to deform the gel through a fixed distance during compression and adhesiveness was defined as the work required to overcome the attractive forces between sample and probe. Hardness and compressibility values from the first and second compression cycles were acceptable when values of coefficients of variation (C.V.) were less than 10%.

Statistical Analysis

All results were evaluated statistically using one-way ANOVA. *Post hoc* statistical analyses of the means of individual groups were performed using Tukey's test. For all analyses, $p < 0.05$ denoted significance.

RESULTS AND DISCUSSION

Gel Preparation

A clear mixture of EC and Miglyol was formed at 60°C. Solidification of the mixture occurred upon cooling to ambient temperature to form an opaque gel. In contrast, preparation of EC gels using Ethocel Med. 100 in diester phthalate solvents by Lizaso *et al.* (11) involved heating to 180°C. The fine EC powders used in the present study probably facilitated the wetting, dispersion and solvation of the polymer particles in Miglyol, thus enabling a lower temperature for gel formation. The gel samples formed were also more homogeneous compared to those formed using coarser EC particles. It was difficult to wet the latter completely, resulting in clumps in the solvent at 60°C.

Continuous Shear Rheometry

Rheograms generated from continuous shear rheometry provided information on the flow pattern and the degree of structural changes in the gel systems upon shearing. In accordance with a Newtonian fluid, liquid paraffin showed a complete overlap of up-curve and down-curve and a directly proportional relationship between shear stress and shear rate with a slope or *n* value approaching unity. This showed that the rheometer and Oswald-de-Waele model were appropriate for the experimental conditions used in this study.

The convex shapes of the rheograms of shear stress vs. shear rate of the EC gels are typical of a shear-thinning system. The decrease in viscosity with increasing shear rate and the presence of hysteresis loops reflected the thixotropic nature of the gel systems (Fig. 1). All the rheograms obtained conformed to the power law relationship of shear stress vs. shear rate, expressed by the Oswald-de-Waele equation ($r > 0.98$). The *n* values of less than 1 for all the gel samples (Table I) indicated shear-thinning behavior (21).

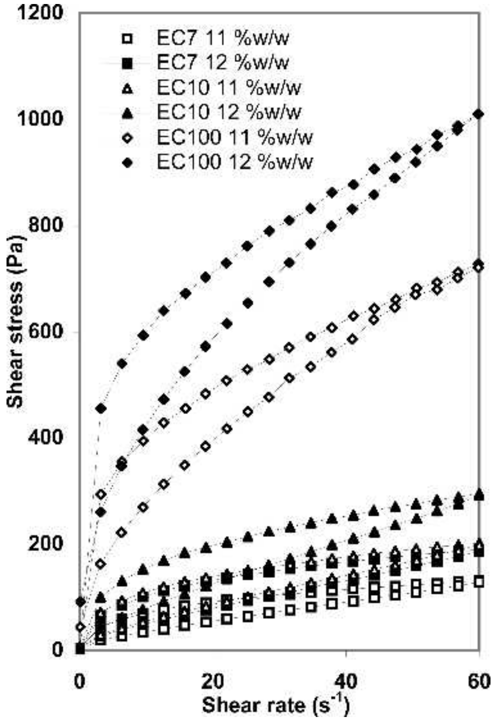


Fig. 1. Rheograms showing thixotropic behavior of EC gels and effects of different EC grades and concentrations on the shear stress and thixotropic breakdown.

The extrapolation of shear stress to zero shear rate in Casson's plot gave the upper limit of the yield stress (22), which is the minimum stress required to be exerted to the gel before it can flow. Yield stress is regarded as a parameter that represents the rigidity and cohesion between molecules forming a three-dimensional gel structure (23).

Increased EC concentration and polymeric chain length resulted in a stronger gel structure, as reflected by the increased yield stress, apparent viscosity at a shear rate of 10 s^{-1} and consistency index values (Table I). The relationship of polymer concentration with yield stress, apparent viscosity and consistency index, respectively, was fairly linear for all the EC gels ($r = 0.9274$ to 0.9709). The concentration dependence of yield stress was observed to increase in the order of EC7 (slope = 19.94) < EC10 (slope = 49.52) < EC100 (slope = 67.48). The apparent viscosity and consistency index values exhibited similar trends. The markedly greater enhancement of yield stress (strength), apparent viscosity and consistency index in EC gels with longer polymeric chains implied that the polymeric chain length exerted a greater influence than the polymer concentrations used in this study.

The hysteresis area (*A*) of the rheogram (Table I), which is associated to the energy required to breakdown the gel structure, was linearly correlated with concentration (*c*) of the gel system as shown by the following equations:

$$A = 653.17c - 5542.5 \qquad (r = 0.9838) \qquad \text{for EC7}$$

$$A = 954.38c - 8443.0 \qquad (r = 0.9925) \qquad \text{for EC10}$$

$$A = 934.02c - 6022.6 \qquad (r = 0.9983) \qquad \text{for EC100}$$

Thixotropic behavior of the EC gels also increased with the increase in polymeric chain length, with the hysteresis areas of 11% and 12% w/w EC100 greater than those of EC7 and EC10 by at least 2.4- and 1.7-fold, respectively. An increase in hysteresis area reflects a more extensive three-dimensional network structure (24). Both larger macromolecules (longer chain length) and higher polymer concentrations allowed the formation of more extensive intermolecular interactions per unit volume, which in turn required higher energy levels to break the network.

Oscillatory Rheometry

The EC formulations exhibited a "gel" mechanical spectrum as $G' > G''$ and $\tan \delta < 1.0$ in both the oscillatory stress sweep and frequency sweep, indicating a predominant elastic behavior (25). This is typical of a structured, three-dimensional physical gel network. In the oscillatory stress sweeps, the stress independence of the shear modulus and tan δ spanned over a wider stress range with an increase in polymeric chain length and concentration. The upper limit of linear viscoelastic behavior ranged from approximately 15 Pa (11% w/w EC7) to 300 Pa (12% w/w EC100). The breaking stress, that is, the stress amplitude when $G'' > G'$ (11), also exhibited similar dependence on polymeric chain length and concentration (Fig. 2). In the viscoelastic region, the polymeric chains were mobilized upon application of shear stress until a critical point was attained, where the polymeric chains were maximally extended. The polymeric chain would even-

Table I. Rheological Properties of EC Gels

EC (%w/w)	Flow behavior index, *n*	Consistency index, k (Pa s^{m})	Apparent viscosity^{a} (mPa s)	Yield stress (Pa)	Hysteresis area (Pa s^{-1})
EC7					
11	0.3612 ± 0.0248	28.51 ± 3.21	7154 ± 768	36.17 ± 6.09	1515 ± 217
12	0.3576 ± 0.0169	44.62 ± 2.82	10359 ± 354	52.51 ± 3.79	2207 ± 211
13	0.3559 ± 0.0053	66.26 ± 2.41	15306 ± 601	77.48 ± 2.72	3066 ± 124
14	0.3754 ± 0.0059	89.2 ± 2.17	21415 ± 373	103.30 ± 2.69	4006 ± 171
15	0.4231 ± 0.0079	95.45 ± 1.35	25623 ± 373	107.09 ± 2.21	4084 ± 49
16	0.4408 ± 0.0039	124.19 ± 2.37	34342 ± 642	137.80 ± 2.78	4772 ± 166
EC10					
11	0.3453 ± 0.0140	49.06 ± 6.6	12225 ± 171	63.08 ± 8.14	2263 ± 147
12	0.3595 ± 0.0194	67.35 ± 3.97	16017 ± 744	85.42 ± 4.86	3064 ± 216
13	0.3760 ± 0.0109	82.34 ± 4.64	19833 ± 1154	102.75 ± 5.79	3727 ± 321
14	0.3830 ± 0.0093	116.44 ± 1.97	28525 ± 1106	142.35 ± 1.90	4660 ± 284
15	0.4047 ± 0.0108	162.54 ± 6.46	41466 ± 1402	200.07 ± 11.44	5838 ± 516
16	0.3771 ± 0.0095	254.01 ± 12.24	60616 ± 1855	333.00 ± 18.36	7093 ± 419
EC100					
7	0.4322 ± 0.0215	12.09 ± 1.37	3250 ± 235	12.80 ± 1.83	575 ± 86
8	0.3386 ± 0.0151	36.95 ± 2.74	8086 ± 361	41.63 ± 3.37	1428 ± 91
9	0.3139 ± 0.0096	75.6 ± 4.74	15589 ± 660	85.19 ± 5.70	2334 ± 175
10	0.3087 ± 0.0055	127.02 ± 4.21	25789 ± 509	143.42 ± 5.03	3363 ± 151
11	0.3125 ± 0.0131	196.62 ± 5.81	40278 ± 790	222.26 ± 7.91	4090 ± 377
12	0.2716 ± 0.0124	322.3 ± 17.85	60600 ± 2607	365.16 ± 19.70	5311 ± 493

[a] Apparent viscosity at a shear rate of 10 s^{-1}.

tually be pulled out of the entangled region with further increase in stress, and hence, begin to slide, resulting in a steep decrease in G′ (26).

The oscillatory frequency sweep test showed a power-law response of log G′ vs. log ω where $G' \propto \omega^{s}$ (ω = radial frequency and *s* = slope of the double logarithmic plot) (Fig. 3). The frequency dependence of G′ in different gel systems could be represented by the values of *s*, where greater degree of structuring in the gel system was reflected by a lower *s* value (27). The *s* values of the EC gels were low, increasing in the order of EC100 (8%w/w and above) < EC10 < EC7, where $s = 0.266$ to 0.277, $s = 0.365$ to 0.372, and $s = 0.375$ to 0.395, respectively. Therefore, degree of gel structuring increased with an increase in polymeric chain length due to the

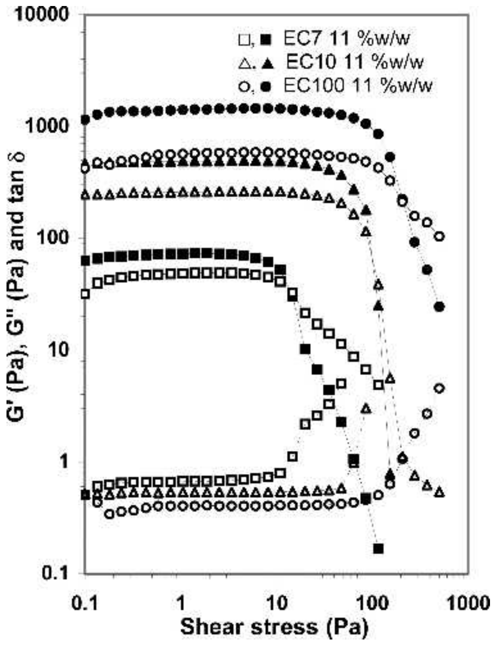


Fig. 2. Storage modulus (G′), loss modulus (G″), and loss tangent (tan δ) as a function of shear stress in the oscillatory stress sweep of EC gels. Closed symbols and solid lines represent G′, open symbols and solid lines represent G″, and open symbols and dotted lines represent tan δ.

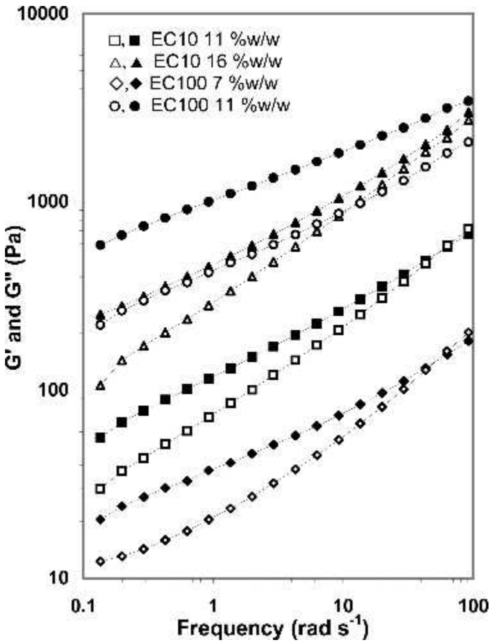


Fig. 3. Storage modulus (G′) and loss modulus (G″) of EC10 and EC100 gels as a function of radial frequency in the oscillatory frequency sweep. Closed symbols represent G′, and open symbols represent G″.

formation of a stronger and more orderly gel network. The *s* value of 7% w/w EC100 was found to be relatively high (s = 0.320) compared to the other concentrations of EC100. This could be attributed to insufficient polymer for extensive intermolecular interactions to produce a strong gel.

EC gels could be classified as physical gels which formed reversible physical crosslinks, as shown by their slight frequency dependence (low *s* values) (28). For a network of entangled polymer chains (pseudogel) (29) or a polymer solution (22), $G'' > G'$ where $G' \propto \omega^2$ and $G'' \propto \omega^1$ at low frequency. On the other hand, the G′ and G″ for a strong, irreversible covalently cross-linked gel are relatively insensitive to frequency (28). In 11–16% w/w EC7, 11–15% w/w EC10, and 7% w/w EC100, there was an obvious crossover of shear moduli at high frequency where $G'' > G'$, as opposed to EC100 (8% w/w and above) where no crossover was apparent even up to the maximum frequency of 100 rad s^{-1} used in the test (Fig. 3). The crossover indicated a transition from a structured physical gel behavior to that of a concentrated polymer solution at high oscillation frequency. The convergence of G′ and G″ curves of 16% w/w EC10 with increasing frequency was consistent with the general behavior of EC10 gels. The change in behavior of EC7 and EC10 gel required very high oscillatory frequency which is unlikely to be encountered under normal situations when a gel is used. Hence, these gels would be deemed to exhibit good rheological properties under normal conditions of use.

The steady shear viscosity, $\eta(\gamma)$ and dynamic viscosity, $\eta^*(\omega)$ profiles obtained for the gels using continuous and oscillatory rheological tests, respectively, were not superimposable, with $\eta^*(\omega) > \eta(\gamma)$ as shown in Fig. 4. The gel systems did not obey Cox-Merz superposition principle for ordinary polymer solutions, which states that the shear rate dependence of $\eta(\gamma)$ is equal to the frequency dependence of $\eta^*(\omega)$, such that $\eta(\gamma)$ and $\eta^*(\omega)$ are superimposable (19,29). This observation reinforced the fact that EC gels formed a more extensive and stronger structural network than just a weak entanglement of polymeric chains.

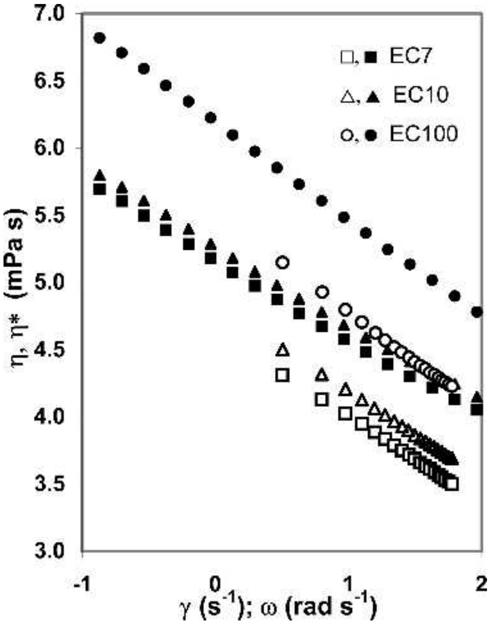


Fig. 4. Combined plots of steady shear viscosity (η) *vs.* shear rate (γ) and dynamic viscosity (η*) *vs.* radial frequency (ω) for 12% w/w of EC7, EC10, and EC100 gels. Closed symbols represent η*, and open symbols represent η.

The effects of polymeric chain length and polymer concentrations on the viscoelastic properties of the gels were statistically evaluated at four representative frequencies (i.e., 0.199, 0.428, 1.987, and 4.281 rad s^{-1}). The EC gel systems generally showed a predictable increase in G′, G″, and η* with increase in EC concentration and polymeric chain length in the order of EC100 > EC10 > EC7, whereas the reverse order applied to tan δ. A lower tan δ value indicates a higher degree of elastic behavior in a gel. Over the representative frequencies used for evaluation, the tan δ for EC100 (8% w/w and above), EC10, and EC7 laid in the respective ranges: 0.400 to 0.479, 0.519 to 0.759, and 0.546 to 0.818. The range of tan δ values for 7% w/w EC100 was particularly high (0.541 to 0.662) compared to those for higher concentrations (8% w/w and above), as the low polymer concentration did not provide sufficient interaction points for the formation of a structured gel. In general, the ranges of tan δ values (less than 1.0) indicated the predominance of elastic behavior over viscous behavior in the EC gels. The observed trends of G′ and tan δ showed that the increased polymeric chain length of EC100 resulted in a higher degree of elastic contribution to the overall character of the gels. From the comparison of average C.V. of G′, G″, tan δ, and η* in the oscillatory frequency range of 0.199 to 62.83 rad s^{-1} for each EC gel sample, tan δ showed the lowest average C.V. (less than 4%). Hence, tan δ could be regarded as a relatively more reliable indicator of the viscoelastic character of the EC gels. Nonetheless, it must be emphasized that the average C.V. values exhibited by other viscoelastic parameters were within an acceptable range (3–15%) with 83% of these values having C.V. <10%.

The polymer concentration-dependent increase in the shear modulus was consistent with the macromolecular entanglement phenomenon where viscoelastic properties increased correspondingly with higher polymer concentrations due to increased entanglement density associated with the number of intermolecular contacts per unit volume (22). The reduced polymer mobility enhanced stability of the system (26). The entanglement density could also be the reason for the significantly more viscous gels with higher polymeric chain lengths as longer chains tend to entangle.

Rheological characterization of topical gels provides crucial information on the gel structure and behavior under different shear and stress conditions. Viscoelastic materials were associated with the ability to withstand mechanical strain (30). Although the correlation of rheological and mechanical properties of EC gels with drug release was not investigated in this study, these properties are expected to have a significant influence on drug release, as observed in other topical gel systems. Difference in rheological behavior between xanthan gum and hydroxypropylmethylcellulose gel matrices has been quoted as the reason for the difference in drug retarding capacity between these matrices (22). Jones *et al.* (31) attributed product viscosity as the basis for the observed drug release behavior of different topical gel formulations containing hydroxyethylcellulose, polyvinylpyrrolidone and polycarbophil. Rheological behavior of poly(acrylic acid) gels has been found to be a highly influential factor affecting mucoadhesion as it serves as an integral part of the detachment process (32). Possession of a gel structure was shown to be favorable for bioadhesion (32,33), which is the prerequisite for effective delivery of drug from any topical dosage form. Rheological and mechanical properties were also found to be a good predictor of the final product performance such as spreading and retention of the gel on its substrate (21). A comparison of the rheological and mechanical properties of the EC gels with those reported in the literature showed that the EC gels are suitable for topical drug delivery.

Mechanical Characterization

In general, there were significant trends ($p < 0.05$) of increasing hardness, compressibility, cohesion and adhesiveness with increased polymer concentrations (Table II and Fig. 5). All four mechanical parameters demonstrated similar profiles.

Linear correlation was obtained between G' at the representative oscillatory frequencies of 0.199, 0.428, 1.987, and 4.281 rad s^{-1}, and the corresponding mechanical properties (i.e., hardness, compressibility, cohesion and adhesiveness), with r values ranging from 0.9292 to 0.9965. The mechanical properties and continuous shear properties i.e., apparent viscosity and yield stress, were better correlated ($r = 0.9611$ to 0.9897) compared to that between mechanical properties and viscoelastic property (G'), as the former could be described by a single regression line irrespective of the grade of EC (Fig. 6). Among the mechanical parameters compared, adhesiveness was best correlated with both viscoelastic and continuous shear properties (Table III). The linear correlations obtained between the rheological and mechanical properties were not unexpected since the relationships between these seemingly unrelated entities have been previously described for aqueous gels (16,32).

The increase in hardness, compressibility, cohesion and adhesiveness values with an increase in EC concentration and polymeric chain length in the order of EC7 < EC10 < EC100 was attributed to the formation of more viscous as well as more elastic gels as indicated by the linear relationship of apparent viscosity and G' with mechanical parameters. EC gels with higher G' presented a stronger and more solid-like structure whereas gels with higher viscosity gave higher resistance to deformation. These resulted in higher compressibility due to the increased work required to move the probe to a certain distance into the gel during compression. Cohesive bonds within the gel matrices would be broken when the probe was lowered into the gel during compression cycle. A more pronounced elastic character would result in higher rate of gel structure recovery after compression through reversible reformation of internal cohesive bonds. This in turn resulted in higher sample tack and increased work done to induce

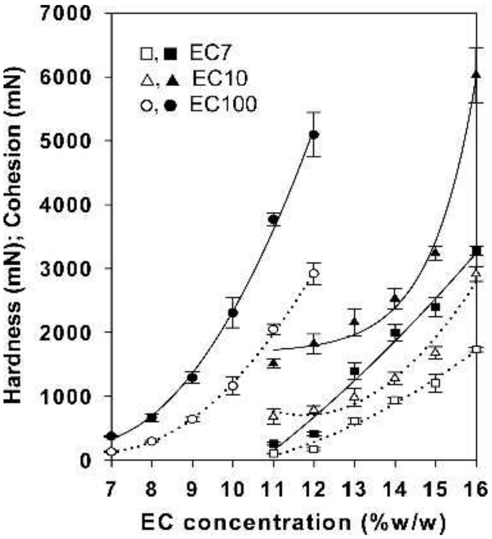


Fig. 5. Change of hardness and cohesion of EC gels with EC concentration. Closed symbols and solid lines represent hardness, and open symbols and dotted lines represent cohesion. Data presented as mean ± SD; n = 3 or 4.

Table II. Mechanical Properties of EC Gels

EC (%w/w)	Hardness (mN)	Compressibility (N mm)	Cohesion (mN)	Adhesiveness (N mm)
EC7				
11	262.50 ± 26.22	3.11 ± 0.28	112.50 ± 3.54	2.98 ± 0.21
12	414.17 ± 31.37	5.25 ± 0.51	180.00 ± 21.21	4.44 ± 0.36
13	1395.00 ± 135.76	17.39 ± 1.62	620.00 ± 43.30	13.38 ± 0.71
14	1993.33 ± 128.56	26.07 ± 2.23	946.67 ± 48.56	20.96 ± 1.46
15	2401.67 ± 150.06	31.20 ± 2.48	1215.00 ± 138.56	26.73 ± 2.59
16	3276.67 ± 69.26	43.39 ± 2.07	1738.33 ± 36.86	36.71 ± 2.53
EC10				
11	1521.88 ± 72.80	19.47 ± 1.47	688.75 ± 123.72	13.40 ± 2.15
12	1828.75 ± 153.73	22.70 ± 1.99	793.75 ± 66.25	16.79 ± 2.15
13	2162.50 ± 211.06	28.52 ± 2.58	991.67 ± 140.12	20.76 ± 3.24
14	2535.63 ± 163.83	33.04 ± 2.91	1288.75 ± 94.46	27.77 ± 1.63
15	3244.17 ± 114.04	42.31 ± 1.86	1688.33 ± 93.05	37.87 ± 1.47
16	6030.83 ± 435.70	76.74 ± 7.40	2921.67 ± 117.30	61.87 ± 5.59
EC100				
7	382.50 ± 11.29	4.84 ± 0.19	140.00 ± 10.00	3.20 ± 0.45
8	674.38 ± 60.56	8.69 ± 0.83	301.25 ± 17.50	7.01 ± 0.18
9	1297.50 ± 90.10	17.13 ± 1.43	648.33 ± 32.53	14.48 ± 0.71
10	2314.00 ± 232.09	29.85 ± 3.75	1168.33 ± 141.89	25.66 ± 3.38
11	3777.50 ± 95.01	49.93 ± 2.19	2055.00 ± 87.18	47.52 ± 3.38
12	5098.13 ± 349.39	67.14 ± 6.55	2926.25 ± 172.31	68.78 ± 5.18

Data presented as mean ± SD.

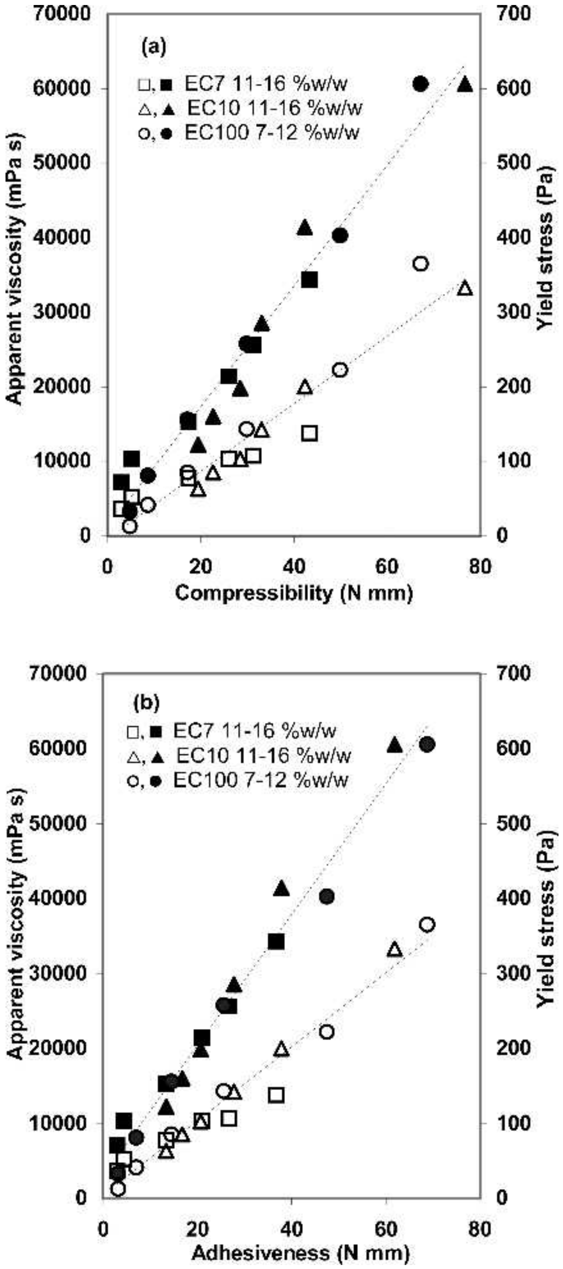


Fig. 6. Continuous shear properties (apparent viscosity and yield stress)–compressibility (a) and continuous shear properties–adhesiveness (b) linear regressions for the entire concentration range of EC gels. Closed symbols represent apparent viscosity, and open symbols represent yield stress.

cleavage of the cohesive bonds upon probe removal from the gel matrices, hence giving rise to higher adhesiveness values (20). Needleman *et al.* (33) has also concluded that presence of a gel structure was indeed favorable for adhesion. Increased adhesiveness was also attributed to the presence of more functional groups for reversible bond formation with the probe surface with higher EC concentration and polymeric chain length.

Each mechanical parameter gives important information on the textural property of the gel, such as ease of gel removal from the container and application onto the substrate as reflected by the hardness and compressibility (34). The latter was regarded as a more convenient measure of gel spreadability as compared to other reported methods which measured the diameter of gel spreading with the application of known weights (15,23). Adhesiveness is an important property for topical dosage forms to ensure product retention or bioadhesion at the site of application (31). It was cited as a reliable gauge for the ability of topical formulations to adhere to nonmucous surfaces such as skin (15), considering the nonmucous nature of the analytical probe used for measurement.

Table III. Rheological-Mechanical Properties Correlation

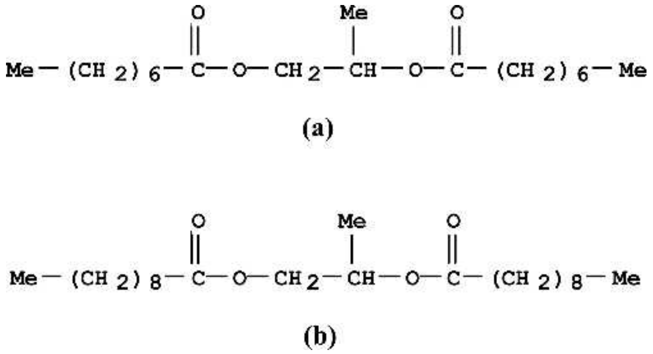
Mechanical parameters	r-value G′ at 0.199 rad/s	Apparent viscosity	Yield stress
Hardness	0.9347	0.9804	0.9611
Compressibility	0.9419	0.9824	0.9625
Cohesion	0.9604	0.9897	0.9747
Adhesiveness	0.9723	0.9896	0.9813

Elucidation of Molecular Interactions Within EC Gels

The interaction forces most likely responsible for entanglement and subsequent gelation of EC include intermolecular hydrogen bonding between the EC polymer molecules, as well as dipole-dipole interaction between the monomer units and solvent molecules. Both types of interaction involved the hydroxyl group at the C-6 position of the anhydroglucose units of the EC backbone (35–38). Diester solvent molecule was postulated to serve as a bridge between EC polymeric chains through dipole-dipole interaction between the positively polarized hydrogen atom on the C-6 hydroxyl group ($^{\delta-}$O-H$^{\delta+}$) of EC and the negatively polarized oxygen atom on the two carbonyl groups ($^{\delta+}$C=O$^{\delta-}$) of the diester solvent molecule and the increase in polymer-polymer interactions gave a favorable effect toward gel elasticity (11).

As the frequency sweep profiles of the reported EC/diester phthalate gels were relatively insensitive to oscillation frequency (11), they formed stronger gel networks than the currently studied EC/diester caprylate or diester caprate gels which were slightly frequency dependent. The observed discrepancy in gel behavior could be explained by considering the molecular conformation of the solvent molecules which might play an influential role in the nature of the solvent-polymer interaction in the EC gel systems.

The solvent used in the present study consisted of propylene glycol diester of caprylic (C_8) and capric (C_{10}) fatty acids which were made up of freely rotating single bonds (Fig. 7) that resulted in higher degree of molecular flexibility than the solvents used by Lizaso *et al.* (11), namely diethyl phthalate, dibutyl phthalate, and di(2-ethylhexyl) phthalate. The diester phthalates are rotationally restricted due to the necessity to maintain planarity with respect to the phenyl ring for effective electron delocalization in order to form stable chemical structures (Fig. 8). Restricted rotation in turn fixed the orientation of the carbonyl groups. Therefore, phthalate molecules were postulated to form more rigid bridges to embrace adjacent EC polymer chains into a closely packed three-dimensional network. When the polymeric chains are held closer together by rigid bridges at certain points, the free nonethoxylated 6-OH groups on the anhydroglucose units



$$\mathrm{Me-(CH_2)_6-\overset{O}{\overset{\|}{C}}-O-CH_2-\overset{Me}{\overset{|}{CH}}-O-\overset{O}{\overset{\|}{C}}-(CH_2)_6-Me}$$

(a)

$$\mathrm{Me-(CH_2)_8-\overset{O}{\overset{\|}{C}}-O-CH_2-\overset{Me}{\overset{|}{CH}}-O-\overset{O}{\overset{\|}{C}}-(CH_2)_8-Me}$$

(b)

Fig. 7. Molecular structures of propylene glycol dicaprylate (a) and dicaprate (b). The freely rotating single bonds served as a basis for molecular flexibility.

along the same polymer chains would be brought to a close proximity, thus facilitating intermolecular hydrogen bonding. On the contrary, the flexibility assumed by the diester caprylate and diester caprate molecules, by virtue of their freely rotating single bonds, rendered the formation of less rigid bridges between the EC polymer chains. These less rigid bridges would impart a certain degree of mobility to the adjacent EC polymer chains, thus compromising the ease of intermolecular hydrogen bond formation. As a result, a less rigid EC gel network formed with propylene glycol dicaprylate/dicaprate than diester phthalates, hence decreasing the elastic modulus and improving the spreadability of the eventual EC gel. Therefore, difference in molecular flexibility of different types of diester solvent would give rise to different conformations and result in an unparalleled degree of bonding within the gel network. Although the proposed conformational flexibility effect of solvent molecules seemed to be able to account for the difference in the dynamic rheological behavior of EC gels, it should be borne in mind that contribution of other factors may not be inconsequential given that different polymer grades and experimental conditions were used in both of these studies.

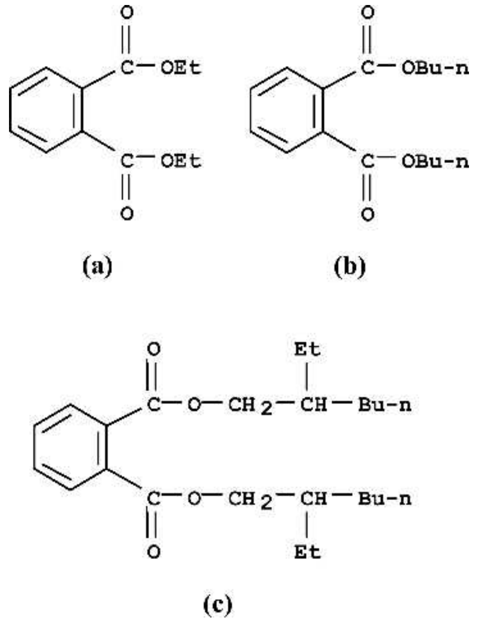


Fig. 8. Molecular structures of diethyl phthalate (a), dibutyl phthalate (b), and di(2-ethylhexyl) phthalate (c) showing the rotationally restricted carbonyl groups due to the presence of phenyl rings.

CONCLUSIONS

Novel nonaqueous gels were developed using three fine particle grades of EC polymer and a diester derivative of propylene glycol. The fine particles of EC allowed the formation of a homogeneous gel at a lower temperature. Gel matrices were successfully prepared from EC of different polymeric chain lengths and concentrations.

The nonaqueous EC gels exhibited rheological profiles that were typical of physically cross-linked three-dimensional gel network, as reflected by their predominant elastic behavior with $G' > G''$ and $\tan \delta < 1.0$, presence of yield stress, and rheograms that showed time-dependent thixotropic behavior. The good correlations observed between rheological parameters such as apparent viscosity, yield stress and elastic modulus, and mechanical parameters underlined the important relationship between rheological and textural properties of the gels. The polymeric chain length and concentration of EC in the formulations influenced the continuous shear properties, viscoelasticity, and mechanical properties of the gels whereby the chain length played a more prominent role. EC100 gels were more stable compared to EC10 and EC7 gels, which exhibited a change to liquid-like behavior at very high oscillatory frequency. The existence and stability of the three-dimensional solid-like gel structure were dependent on the balance between two types of interaction forces within the EC gel network, that is, intermolecular hydrogen bonding between the polymer chains, and dipole-dipole interactions between polymer and solvent molecules. Molecular conformation of the solvent was postulated to play a crucial role in determining the strength of solvent-polymer interaction, which in turn affected the ease of intermolecular hydrogen bond formation between the EC chains. The rheological and mechanical properties of the EC gel matrices showed that they are potentially useful as a vehicle for topical drug delivery.

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