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Rheological, mechanical and mucoadhesive properties of thermoresponsive, bioadhesive binary mixtures composed of poloxamer 407 and carbopol 974P designed as platforms for implantable drug delivery systems for use in the oral cavity

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ABSTRACT

This study described the formulation and characterisation of the viscoelastic, mechanical and mucoadhesive properties of thermoresponsive, binary polymeric systems composed of poloxamer (P407) and poly(acrylic acid, C974P) that were designed for use as a drug delivery platform within the oral cavity. Monopolymeric and binary polymeric formulations were prepared containing 10, 15 and 20% (w/w) poloxamer (407) and 0.10–0.25% (w/w) poly(acrylic acid, 934P). The flow rheological and viscoelastic properties of the formulations were determined using controlled stress and oscillatory rheometry, respectively, the latter as a function of temperature. The mechanical and mucoadhesive properties (namely the force required to break the bond between the formulation and a pre-hydrated mucin disc) were determined using compression and tensile analysis, respectively. Binary systems composed of 10% (w/w) P407 and C934P were elastoviscous, were easily deformed under stress and did not exhibit mucoadhesion. Formulations containing 15 or 20% (w/w) Pluronic P407 and C934P exhibited a sol–gel temperature $T_{sol/gel}$, were viscoelastic and offered high elasticity and resistance to deformation at 37 °C. Conversely these formulations were elastoviscous and easily deformed at temperatures below the sol–gel transition temperature. The sol–gel transition temperatures of systems containing 15% (w/w) P407 were unaffected by the presence of C934P; however, increasing the concentration of C934P decreased the $T_{sol/gel}$ in formulations containing 20% (w/w) P407. Rheological synergy between P407 and C934P at 37 °C was observed and was accredited to secondary interactions between these polymers, in addition to hydrophobic interactions between P407 micelles. Importantly, formulations composed of 20% (w/w) P407 and C934P exhibited pronounced mucoadhesive properties. The ease of administration (below the $T_{sol/gel}$) in conjunction with the viscoelastic (notably high elasticity) and mucoadhesive properties (at body temperature) render the formulations composed of 20% (w/w) P407 and C934P as potentially useful platforms for mucoadhesive, controlled topical drug delivery within the oral cavity.

1. Introduction

Topical drug delivery is frequently utilised for the treatment of localised disorders, e.g. periodontal disease, infection within the oral cavity. The main advantages of this mode of drug delivery are the ability to deliver the bioactive agent directly to the site and the maintenance of the required concentration of drug at the site for a prolonged period (Jones et al., 2000). However, one problem that is exhibited by many topical implantable systems is poor retention, due primarily to both the limited interaction of the implant with the host epithelium and mechanical removal due the action of body fluids, mucosal turnover and the applied stresses during processes such as chewing and swallowing (Jones et al., 1999, 2000; Edsman and Hagerstrom, 2005; Smart, 2005). The ability of the bioactive implant to be retained at the site of application is therefore a key design parameter of such systems.

Bioadhesion refers to the interaction of a polymeric platform with a biological substrate, the term mucoadhesion being used whenever the biological substrate is coated with mucus (Woolfson et al., 2002; Edsman and Hagerstrom, 2005). The application of bioadhesive/mucoadhesive systems therefore presents a possible method by which the retention of dosage forms at the site of

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application may be enhanced. Whilst several theories have been proposed to describe bioadhesion, it is generally accepted that the adhesive interaction between the polymeric system and the mucus-covered substrate is facilitated by initial wetting of the dosage form on the biological substrate, followed by the interpenetration of the polymeric chains within the implant into the mucus layer (Woolfson et al., 2002; Smart, 2005). At this stage secondary bond formation (e.g. van der Waals/hydrogen bonding) occurs that maintains the intimate contact between the two surfaces (Woolfson et al., 2002). The bioadhesive properties of formulations may be modified by selection of the polymeric components due to the importance of chemical structure on the bioadhesive interaction (Woolfson et al., 2002). It has been reported that the mucoadhesive properties of dosage forms is, in part, dependent on the state of the bio/mucoadhesive polymer within the final product (Woolfson et al., 2002). Consequently, the bioadhesive properties of formulations in which the (bioadhesive) polymers are fully hydrated, e.g. solutions, dilute gels will be markedly less than those in which the bioadhesive component is dispersed within a vehicle or ultimately those in which the dosage form is solid in nature, e.g. films or compacts (Jones et al., 2000; Woolfson et al., 2002; Irwin et al., 2003). Accordingly, in systems where hydration of the bioadhesive component has occurred within the dosage form, the bioadhesive interactions are lower due to the limited inability of the polymer to diffuse into and subsequently interact with mucin. Conversely, in systems where the bioadhesive components are presented as solids (e.g. compacts) or in systems where there is limited aqueous fluid (e.g. semi-solids, films), contact with mucin facilitates polymer chain hydration and expansion, leading to deep penetration into and interaction with mucin. The substantial bioadhesive properties of this latter class of bioadhesive systems has been proven, both *in vitro* and *in vivo* (Woolfson et al., 1995; Jones et al., 1999, 2000; Irwin et al., 2003). In addition to the state of the bioadhesive polymer within the pharmaceutical implant, the rheological properties of the formulation have been reported to play an important role in product retention. For example Tamburic and Craig (1995) and the authors (Jones et al., 2000, 2001) have described the relationship between the viscoelastic properties of pharmaceutical systems, in particular the elastic properties, and adhesion to mucin. Therefore, in addition to possessing the optimal presentation of the bioadhesive polymer to mucin, the rheological properties of formulations should be engineered to offer optimal elasticity (high storage modulus and low loss tangent) to offer resistance to detachment and removal from the site of application.

The development of pharmaceutical systems that may be implanted into a selected body cavity and offer retention at the site of application still remains a significant challenge. In certain applications, the retention of implants may be further compromised by difficulties surrounding the insertion process. For example, eye drop formulations are required to flow onto the conjunctiva as a droplet under the force of gravity whereas; formulations that are designed for application into the periodontal pocket for the treatment of periodontal disease must successfully flow into the pocket through the fine orifice of a periodontal syringe. Under these design restrictions, the rheological properties that would have been beneficial to assist retention at the site of application are compromised, which may, in turn, affect the *in situ* retention. One strategy by which this problem may be overcome involves the formulation of implants whose rheological properties are temperature dependent, rheological structuring occurring at body temperature, and which, in addition, offer bioadhesive properties. Therefore in this study, the rheological and mucoadhesive properties of binary polymeric systems, designed as platforms for local drug delivery and composed of a block co-polymer of poly(oxyethylene) and poly(oxypropylene) and poly(acrylic acid) are presented. It is proposed that these systems will offer rheological structuring and mucoadhesion at body temperature and thereby resolve, at least in part, the aforementioned problems. A comprehensive examination of the rheological properties of these systems has been described to gain a greater understanding of the interaction between these polymers and, in addition, to evaluate the effects of a wide range of stresses (both during application and *in situ*) that these prototype systems will experience. This information will enable the potential suitability of these systems for the proposed application to be discerned.

2. Materials and methods

2.1. Chemicals

Poloxamer 407 (Pluronic F127) and polyacrylic acid (carbopol 934P) were purchased from Sigma (St. Louis, MO, USA) and from B.F. Goodrich (Brecksville, OH, USA), respectively. Triethanolamine (TEA), purchased from Galena (Campinas, SP, Brasil) was used as a neutralising agent.

2.2. Preparation of semi-solid formulations

Monopolymeric systems were manufactured containing poloxamer 407 (P407; 10, 15, or 20%, w/w) or carbopol 934P (C934P; 0.10, 0.15, 0.20, or 0.25%, w/w). Poloxamers were prepared by dissolving the required amount of P407 in distilled water at 5 °C under gentle agitation (500 rpm) using a mechanical stirrer (Heidolph), as previously reported by the authors (Jones et al., 2003a). Aqueous poly(acrylic acid) gels were prepared by gradually dissolving the required mass in distilled water, with vigorous mechanical stirring (Heidolph, 2000 rpm) and subsequent neutralisation with triethanolamine (Jones et al., 1997a,b).

Twelve binary polymer systems were manufactured containing P407 (10, 15, or 20%, w/w) and C934P (0.10, 0.15, 0.20, or 0.25%, w/w). The required mass of C934P was initially dissolved in distilled water (at 5 °C) using a mechanical stirrer, following which the required mass of poloxamer was added to this gel and stirred to ensure complete mixing. The resultant gels were neutralised by the addition of TEA, centrifuged at 3000 rpm to remove entrapped air and stored at 4 °C for at least 24 h prior to further analysis.

2.3. Continuous shear (flow) rheometry

Continuous shear analysis of each formulation was performed at 5 and 37 ± 0.1 °C using a AR 2000 controlled stress rheometer (T.A. Instruments, Surrey, England), in flow mode, and in conjunction with parallel steel plate geometry (40 mm, separated by a fixed distance of 1.0 mm) or with standard-size double concentric cylinders geometry, rotor outer radius of 21.96 mm and inner radius of 20.38 mm, stator inner radius of 20.00 mm, cylinder height of 59.50 mm, and gap of 0.5 mm, according to the consistency of each formulation. Samples were carefully applied to the lower plate or to the inside stator of the concentric cylinder geometry, ensuring that formulation shearing was minimized, and allowed to equilibrate for at least 5 min prior to analysis. Upward and downward flow curves were measured over a range of shear rates (10–10,000 s^{-1}). In each case, the shearing rate was increased over a period of 150 s, held at the upper limit for 10 s, and then decreased over a period of 150 s. Selection of the range of shear rates was performed according to the consistency of each formulation. The flow properties of at least five replicate samples were determined and the upward flow curves were modelled using the Oswald-de-Waele equation (power law;

Eq. (1)) (Jones et al., 2002):

$$\sigma = k\gamma^n \quad (1)$$

where σ is the shear stress (Pa), k is the consistency index ((Pa s)^n), γ is the rate of shear (s^{-1}), and n is the flow behaviour index (dimensionless).

2.4. Oscillatory rheometry

Oscillatory rheometry of all formulations was performed using a AR 2000 controlled stress rheometer (T.A. Instruments, Surrey, England) in oscillation mode at 5 and 37 ± 0.1 °C. The correct geometry was selected according to the rheological properties of the various formulations and accordingly, either a 40 mm parallel steel plate (separated by a fixed distance of 1.0 mm) or standard-size double concentric cylinders (rotor outer radius of 21.96 mm and inner radius of 20.38 mm, stator inner radius of 20.00 mm, height cylinder of 59.50 mm, and gap of 0.5 mm), were employed (Jones et al., 2002). Samples of each formulation were carefully applied to the lower plate or to the inside stator of the rheometer as described previously. After determination of the linear viscoelastic region of each formulation, i.e. the region in which stress was directly proportional to strain and the storage modulus (G') remained constant, frequency sweep analysis was performed over the frequency range of 0.1–10.0 Hz following application of a constant stress. The storage modulus (G'), loss modulus (G''), dynamic viscosity (η') and the loss tangent ($\tan\delta$) were then calculated using Rheology Advantage software provided by T.A. Instruments. In each case the dynamic rheological properties of at least five replicate samples were determined.

Examination of the possible interaction between P407 and C934P in the binary polymer systems was determined as previously reported (Hassan and Gallo, 1990; Andrews et al., 2005; Andrews and Jones, 2006). This method assesses the difference between the dynamic modulus of the mixture and the theoretical value of the modulus obtained by summation of the individual parts. Calculation of the interaction parameter for the binary mixtures was determined using the storage modulus values at an oscillatory frequency of 10.0 Hz as follows (Eq. (2)):

$$\Delta G' = G'_{\mathrm{mix(P407/C934P)}} - (G'_{\mathrm{P407}} + G'_{\mathrm{C934P}}) \quad (2)$$

2.5. Determination of the sol–gel temperature ($T_{sol/gel}$) using oscillatory rheometry

The determination of the sol–gel temperature was performed using oscillatory rheometry as previously reported (Jones et al., 2003a), using parallel plate or concentric cylinder geometries, as described above. As before, samples of each formulation were carefully applied to the lower plate or to the inside stator of the rheometer, ensuring that the formulation shearing was minimized, and allowed to equilibrate for at least 5 min prior to analysis. After determination of the linear viscoelastic region of each formulation (at 5 and 60 °C), a linear temperature sweep analysis was performed over the temperature range of 5–60 °C at a defined frequency (1 Hz) and rate of heating 10 °C min^{-1}) using a controlled stress (resident within the linear viscoelastic region). The storage modulus (G'), loss modulus (G''), dynamic viscosity (η') and the loss tangent ($\tan\delta$) were calculated using the proprietary software, as described above. $T_{\mathrm{sol/gel}}$ was defined as the temperature at which the elastic modulus was halfway between the values for the solution and for the gel and was calculated for all systems in which dynamic viscosity increased with increasing temperature (Edsman et al., 1998; Ricci et al., 2002; Tosh and Marangoni, 2004). The sol–gel temperature of at least five replicate samples was examined in all cases.

2.6. Evaluation of compressional flow

The compressional flow of all formulations was determined using a TA-XTplus Texture Analyser (Stable Micro Systems, Surrey, England) in compression mode, as previously described (Jones et al., 2002; Andrews et al., 2005). Formulations (16 g) were packed into McCartney bottles and centrifuged to remove entrapped air. Following this, an analytical probe (10 mm diameter) was twice compressed into each sample at a defined rate (2 mm s^{-1}) and to a defined depth (15 mm). At least five replicate analyses of each sample were performed at both 5 and 37 °C. From the relationship between force and distance, the compressibility (the work required to deform the product during the first compression of the probe) and the hardness (the maximum force during compression) were calculated (Jones et al., 2002; Andrews et al., 2005).

2.7. Evaluation of the mucoadhesive properties

The mucoadhesive strength of the various binary polymer systems was evaluated by measuring the force required to detach the formulations from a partially hydrated mucin disc using a TA-XTplus Texture Analyser (Stable Micro Systems, Surrey, England) in tension mode (Jones et al., 1999, 2000). Initially, mucin discs were prepared by compression of porcine mucin (250 mg) for 30 s using a ring press with a 13 mm diameter die and a defined compression force (10 tonnes). These discs were then horizontally attached to the lower end of the TPA probe using double-sided adhesive tape. Prior to mucoadhesion testing, the mucin disc was hydrated by submersion in a 5% solution of mucin for 30 s following by gentle blotting. Samples of each formulation, previously packed into shallow cylindrical vessels and stored at 37 °C, were placed under the analytical probe, which was then lowered until the mucin disc contacted the surface of the sample. A downward force of 0.1 N was applied for 30 s, the probe was then moved upwards at a constant speed of 1.0 mm s^{-1} and the force required to detach the mucin disc from the surface of each formulation determined as the maximum value in the resultant relationship between force and distance. All measurements were performed for at least five times.

2.8. Statistical analysis

The effects of polymer concentration, polymer type, and temperature on the consistency index and the flow index (both derived from the power law model) and the viscoelastic properties (G', G'', $\tan\delta$, and η') at five representative frequencies (0.60, 2.55, 5.04, 7.53, and 10.0 Hz) were statistically compared using a three-way analysis of variance (ANOVA). Similarly, the effects of concentrations of P407 and C934P, and temperature on compressional flow properties were statistically evaluated using three-way ANOVA. Furthermore, the effects of the type and concentration of each polymeric component on the force required to overcome the mucin-formulation adhesive bond were statistically evaluated using two-way ANOVA. Individual differences between means were identified using Tukey's honestly significant difference test. The paired Student's t-test was used to determine if the dynamic viscosity of the formulations was significantly increased with increasing temperature increasing (gelation). Finally, statistical comparison of the modulus of binary mixtures and the theoretical modulus following addition of the individual moduli were performed using an unpaired t-test. In all cases, a significance level of $p < 0.05$ was accepted to denote significance (Jones, 2002).

3. Results

In continuous shear rheometry, the P407-monopolymeric systems exhibited flow behaviour that was dependent on both the

Table 1
The effects of concentration of polymer (C934P, P407, %, w/w) and temperature on the consistency (k) and rheological exponent (n) of monopolymeric and binary polymeric systems.

Conc. of P407 (%)	Conc. of C934P (%)	k (Pa s)^n at °C		n (dimensionless) at °C	
		5 °C	37 °C	5 °C	37 °C
10	0	0.01 ± 0.00	0.01 ± 0.00	0.97 ± 0.02	0.99 ± 0.02
15	0	0.02 ± 0.00	0.14 ± 0.03	0.97 ± 0.01	0.87 ± 0.02
20	0	0.04 ± 0.00	183.48 ± 3.45	0.97 ± 0.00	0.12 ± 0.00
0	0.10	0.16 ± 0.01	0.07 ± 0.00	0.71 ± 0.01	0.72 ± 0.00
0	0.15	0.56 ± 0.03	0.32 ± 0.06	0.62 ± 0.01	0.63 ± 0.00
0	0.20	2.23 ± 0.02	1.50 ± 0.07	0.53 ± 0.00	0.52 ± 0.00
0	0.25	9.98 ± 0.11	10.64 ± 0.15	0.42 ± 0.00	0.37 ± 0.00
10	0.10	0.09 ± 0.00	0.08 ± 0.00	0.86 ± 0.00	0.87 ± 0.00
10	0.15	0.31 ± 0.00	0.30 ± 0.02	0.77 ± 0.00	0.78 ± 0.00
10	0.20	1.11 ± 0.04	1.14 ± 0.11	0.67 ± 0.00	0.67 ± 0.01
10	0.25	3.23 ± 0.11	3.50 ± 0.05	0.59 ± 0.00	0.59 ± 0.00
15	0.10	0.14 ± 0.01	16.04 ± 1.08	0.88 ± 0.01	0.42 ± 0.01
15	0.15	0.36 ± 0.00	42.45 ± 3.73	0.80 ± 0.00	0.33 ± 0.02
15	0.20	1.13 ± 0.03	35.93 ± 3.32	0.72 ± 0.00	0.38 ± 0.02
15	0.25	2.67 ± 0.07	30.39 ± 2.93	0.64 ± 0.01	0.42 ± 0.02
20	0.10	0.18 ± 0.00	219.84 ± 5.50	0.89 ± 0.00	0.20 ± 0.00
20	0.15	0.39 ± 0.00	267.76 ± 8.13	0.83 ± 0.00	0.22 ± 0.00
20	0.20	0.99 ± 0.06	362.88 ± 6.62	0.78 ± 0.00	0.18 ± 0.00
20	0.25	1.95 ± 0.05	437.02 ± 42.62	0.71 ± 0.00	0.18 ± 0.00

concentration of polymer and temperature. Newtonian flow was exhibited by formulations composed of 10% (w/w) P407 (at all temperatures) as well those composed of 15 and 20% (w/w) polymer at 5 °C. At 37 °C formulations composed of either 15 or 20% (w/w) P407 exhibited shear-thinning behaviour (pseudoplastic flow). At all concentrations the C934P monopolymeric systems exhibited pseudoplastic behaviour with various degrees of thixotropy that were dependent on polymer concentration and temperature.

The formulations containing binary mixtures of P407 and C934P exhibited pseudoplastic behaviour with various degrees of thixotropy at each temperature under examination. To enable statistical comparisons of the effects of each polymeric component on the flow properties of the formulations, the up-curve of each rheogram was mathematically defined using the power law model (Eq. (1)) from which the consistency and flow index of each formulation were derived (Table 1) (Jones et al., 2002). As the concentration of polymer and temperature were increased, the consistency and flow index increased and decreased, respectively. In monopolymeric gels composed of C934P, there was a significant increase in the consistency and reduction in the flow index as the concentration was increased. Increasing the temperature of these systems resulted in a decrease in the consistency whereas the flow index was unaffected. The steady shear behaviour of the binary polymer systems was similarly influenced by both the temperature and the concentrations of each polymer, with the exception of binary systems containing 10% poloxamer in which thermoresponsive rheological behaviour was not observed. There was a significant increase in the consistency as the concentrations of each polymeric component and temperature were increased. In contrast, the flow behaviour index was significantly decreased. Increasing the concentration of each polymer sequentially increased the consistency of the formulations whereas increasing the temperature decreased the flow index of all binary formulations composed of 15 and 20% (w/w) P407.

The effects of polymer concentration and temperature on the viscoelastic properties, namely, storage modulus (G'), loss modulus (G''), dynamic viscosity (η'), and loss tangent ($\tan\delta$), of all primary systems and binary polymer systems at five selected oscillatory frequencies are displayed in Fig. 1 and Tables 2–6. The viscoelastic properties of C934P-only formulations also were temperature, polymer concentration, and frequency dependent (Table 2). Typically, increasing the temperature significantly decreased the dynamic viscosity, storage and loss moduli, whereas the loss tangent significantly increased. Furthermore, increasing the oscillatory frequency significantly increased the storage and loss moduli, whereas the dynamic viscosity significantly decreased. The effect of oscillatory frequency on the loss tangent was temperature dependent. For example, increasing the oscillatory frequency from 0.6 to 10.0 Hz, increased the storage modulus of the formulation composed of 0.20% (w/w) C934P from 39.17 ± 1.74 to 52.06 ± 2.05 Pa at 5 °C and from 32.80 ± 1.64 to 40.10 ± 2.01 Pa at 37 °C. Moreover, increasing the C934P concentration significantly increased the dynamic viscosity, storage and loss moduli, whereas the loss tangent significantly decreased as the concentration increased. The storage modulus exceeded the loss modulus across the entire frequency range (0.6–10.0 Hz), with the exception of formulations composed of 0.10% (w/w) C934P.

Primary systems composed of P407 displayed storage and loss moduli that were temperature, polymer concentration, and frequency dependent (Table 3). Typically, increasing the temperature and the oscillatory frequency significantly increased the storage and loss moduli, whereas the loss tangent significantly decreased. For example, increasing the oscillatory frequency from 0.6 to 10.0 Hz, increased the storage modulus of the formulation composed of 15% (w/w) P407 from 0.01 ± 0.00 to 0.06 ± 0.00 Pa at 5 °C and from 19.61 ± 0.67 to 37.85 ± 0.50 Pa at 37 °C. Moreover, the dynamic viscosity was significantly increased as the temperature increased and significantly decreased with increasing frequency. The rheological

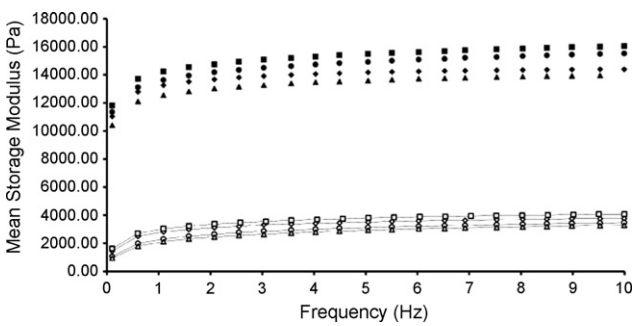

Fig. 1. The effect of poloxamer concentration (closed figures 20% w/w, open figures 15% w/w) and polyacrylic acid concentration (diamonds 0.10% w/w, squares 0.15% w/w. circles 0.20% w/w and triangles 0.20% w/w) on the storage modulus of binary gels (at 37 °C).

Table 2
The effects of concentration of poly(acrylic acid) (C934P) and temperature on the viscoelastic properties at five representative frequencies.

C934P Conc. (% w/w)	Oscillatory frequency (Hz)	Mean (±S.D.) viscoelastic properties at 5 °C				Mean (±S.D.) viscoelastic properties at 37 °C			
		G' (Pa)	G'' (Pa)	tan δ	η' (Pa s)	G' (Pa)	G'' (Pa)	tan δ	η' (Pa s)
0.10	0.60	0.04 ± 0.00	0.11 ± 0.01	3.05 ± 0.16	0.03 ± 0.00	0.02 ± 0.00	0.06 ± 0.00	3.09 ± 0.11	0.02 ± 0.00
0.10	2.55	0.16 ± 0.00	0.24 ± 0.01	14.62 ± 0.69	0.01 ± 0.00	0.02 ± 0.00	0.11 ± 0.00	5.27 ± 0.04	0.01 ± 0.00
0.10	5.04	0.04 ± 0.00	0.49 ± 0.04	12.94 ± 1.17	0.02 ± 0.00	0.06 ± 0.00	0.24 ± 0.00	4.10 ± 0.02	0.01 ± 0.00
0.10	7.53	0.03 ± 0.00	0.75 ± 0.05	31.20 ± 2.03	0.02 ± 0.00	0.07 ± 0.00	0.38 ± 0.00	5.86 ± 0.02	0.01 ± 0.00
0.10	10.00	0.02 ± 0.00	1.03 ± 0.08	82.63 ± 6.33	0.02 ± 0.00	0.04 ± 0.00	0.53 ± 0.00	14.63 ± 0.05	0.01 ± 0.00
0.15	0.60	2.39 ± 0.06	1.22 ± 0.03	0.51 ± 0.00	0.33 ± 0.01	1.05 ± 0.05	0.83 ± 0.02	0.79 ± 0.04	0.22 ± 0.00
0.15	2.55	3.42 ± 0.07	2.39 ± 0.04	0.70 ± 0.00	0.15 ± 0.00	1.71 ± 0.01	1.21 ± 0.06	0.70 ± 0.03	0.07 ± 0.00
0.15	5.04	4.07 ± 0.08	3.60 ± 0.05	0.89 ± 0.00	0.11 ± 0.00	2.06 ± 0.00	1.59 ± 0.05	0.77 ± 0.02	0.05 ± 0.00
0.15	7.53	4.54 ± 0.07	4.67 ± 0.06	1.03 ± 0.00	0.10 ± 0.00	2.49 ± 0.02	1.95 ± 0.03	0.78 ± 0.02	0.04 ± 0.00
0.15	10.00	4.91 ± 0.05	5.64 ± 0.06	1.15 ± 0.00	0.09 ± 0.00	2.90 ± 0.01	2.31 ± 0.04	0.80 ± 0.01	0.04 ± 0.00
0.20	0.60	39.17 ± 0.25	4.41 ± 0.15	0.11 ± 0.00	1.18 ± 0.15	32.80 ± 1.85	2.98 ± 0.15	0.09 ± 0.01	0.80 ± 0.04
0.20	2.55	43.40 ± 0.31	8.82 ± 0.13	0.20 ± 0.00	0.55 ± 0.01	35.40 ± 2.00	5.11 ± 0.27	0.14 ± 0.00	0.32 ± 0.02
0.20	5.04	48.81 ± 0.47	12.70 ± 0.13	0.27 ± 0.00	0.40 ± 0.00	37.34 ± 1.94	7.26 ± 0.39	0.19 ± 0.00	0.23 ± 0.01
0.20	7.53	49.59 ± 0.49	15.77 ± 0.12	0.32 ± 0.00	0.33 ± 0.00	38.82 ± 1.90	9.01 ± 0.43	0.23 ± 0.00	0.19 ± 0.01
0.20	10.00	52.06 ± 0.54	18.44 ± 0.10	0.35 ± 0.00	0.29 ± 0.00	40.10 ± 1.85	10.56 ± 0.48	0.26 ± 0.01	0.17 ± 0.01

Table 3
The effects of concentration of poloxamer and temperature on the viscoelastic properties at five representative frequencies.

Poloxamer Conc. (% w/w)	Oscillatory frequency (Hz)	Mean (±S.D.) viscoelastic properties at 5 °C				Mean (±S.D.) viscoelastic properties at 37 °C			
		G' (Pa)	G'' (Pa)	tan δ	η' (Pa s)	G' (Pa)	G'' (Pa)	tan δ	η' (Pa s)
10.00	0.60	0.01 ± 0.00	0.04 ± 0.00	94.71 ± 4.57	0.01 ± 0.00	2.89 ± 0.02	1.49 ± 0.00	0.51 ± 0.00	0.40 ± 0.00
10.00	2.55	0.01 ± 0.00	0.17 ± 0.00	40.65 ± 3.77	0.01 ± 0.00	5.52 ± 0.16	1.68 ± 0.17	0.30 ± 0.02	0.10 ± 0.01
10.00	5.04	0.01 ± 0.00	0.34 ± 0.00	27.43 ± 7.75	0.01 ± 0.00	9.01 ± 0.09	1.60 ± 0.15	0.18 ± 0.01	0.05 ± 0.00
10.00	7.53	0.03 ± 0.00	0.52 ± 0.00	19.39 ± 0.61	0.01 ± 0.00	12.40 ± 0.13	1.81 ± 0.11	0.15 ± 0.01	0.04 ± 0.00
10.00	10.00	0.06 ± 0.00	0.70 ± 0.01	12.74 ± 0.56	0.01 ± 0.00	15.73 ± 0.02	2.09 ± 0.13	0.13 ± 0.01	0.03 ± 0.00
15.00	0.60	0.01 ± 0.00	0.08 ± 0.00	88.36 ± 5.06	0.02 ± 0.00	19.61 ± 0.67	5.28 ± 0.28	0.27 ± 0.02	1.41 ± 0.07
15.00	2.55	0.01 ± 0.00	0.36 ± 0.00	59.01 ± 1.23	0.02 ± 0.00	24.63 ± 0.71	3.59 ± 0.07	0.15 ± 0.01	0.22 ± 0.00
15.00	5.04	0.02 ± 0.00	0.70 ± 0.01	40.11 ± 3.51	0.02 ± 0.00	29.53 ± 0.69	3.91 ± 0.12	0.13 ± 0.01	0.12 ± 0.00
15.00	7.53	0.03 ± 0.00	1.05 ± 0.03	33.19 ± 0.85	0.02 ± 0.00	33.81 ± 0.04	4.65 ± 0.29	0.14 ± 0.01	0.10 ± 0.01
15.00	10.00	0.06 ± 0.00	1.40 ± 0.03	22.06 ± 1.52	0.02 ± 0.00	37.85 ± 0.50	5.50 ± 0.38	0.15 ± 0.01	0.09 ± 0.01
20.00	0.60	0.01 ± 0.00	0.15 ± 0.00	129.28 ± 11.30	0.04 ± 0.00	13130.00 ± 306.59	456.92 ± 32.62	0.03 ± 0.00	229.10 ± 11.33
20.00	2.55	0.01 ± 0.00	0.65 ± 0.00	101.75 ± 4.30	0.04 ± 0.00	13522.00 ± 329.17	460.18 ± 22.53	0.03 ± 0.00	28.75 ± 1.40
20.00	5.04	0.02 ± 0.00	1.27 ± 0.01	77.56 ± 1.03	0.04 ± 0.00	13750.00 ± 338.23	443.62 ± 22.25	0.03 ± 0.00	10.84 ± 0.38
20.00	7.53	0.04 ± 0.00	1.90 ± 0.02	46.45 ± 1.50	0.04 ± 0.00	13756.02 ± 343.12	389.02 ± 18.54	0.03 ± 0.00	5.79 ± 0.42
20.00	10.00	0.14 ± 0.00	2.53 ± 0.03	18.15 ± 0.62	0.04 ± 0.00	13696.05 ± 333.44	402.58 ± 26.87	0.03 ± 0.00	3.63 ± 0.14

behaviour of the P407-only systems also changed as a function of polymer concentration. Increasing of the P407 concentration from 10–15 to 20% (w/w) significantly increased the dynamic viscosity, storage and loss moduli. At 5 °C, the loss modulus exceeded the storage modulus at all P407 concentrations whereas, conversely, at 37 °C the loss tangent was less than unity across the entire frequency range (0.6–10.0 Hz).

The loss modulus (G''), dynamic viscosity (η''), and loss tangent (tan δ) of the various binary polymer systems at three temperatures and five selected oscillatory frequencies are displayed in Tables 4–6.

Table 4
The effect of concentration of poly(acrylic acid) (C934P) and temperature on the viscoelastic properties of binary systems containing 10% (w/w) poloxamer 407 at five representative frequencies.

Conc. of C934P (%w/w)	Oscillatory frequency (Hz)	Mean (±S.D.) viscoelastic properties at 5 °C			Mean (±S.D.) viscoelastic properties at 37 °C		
		η' (Pa s)	G'' (Pa)	tan δ	η' (Pa s)	G'' (Pa)	tan δ
0.10	0.60	0.07 ± 0.00	0.27 ± 0.00	2.68 ± 0.00	0.18 ± 0.02	0.69 ± 0.07	0.74 ± 0.03
0.10	2.55	0.05 ± 0.00	0.79 ± 0.00	3.53 ± 0.00	0.08 ± 0.01	1.36 ± 0.10	0.63 ± 0.06
0.10	5.04	0.05 ± 0.00	1.49 ± 0.00	4.35 ± 0.00	0.07 ± 0.00	2.19 ± 0.10	0.58 ± 0.04
0.10	7.53	0.05 ± 0.00	2.19 ± 0.00	5.41 ± 0.00	0.06 ± 0.00	2.94 ± 0.08	0.53 ± 0.02
0.10	10.00	0.05 ± 0.00	2.85 ± 0.00	6.87 ± 0.00	0.06 ± 0.00	3.68 ± 0.04	0.51 ± 0.03
0.15	0.60	0.17 ± 0.01	0.63 ± 0.03	3.36 ± 0.15	0.17 ± 0.01	0.65 ± 0.02	1.44 ± 0.07
0.15	2.55	0.13 ± 0.01	2.14 ± 0.12	3.41 ± 0.19	0.12 ± 0.01	2.02 ± 0.14	1.89 ± 0.12
0.15	5.04	0.11 ± 0.01	3.65 ± 0.16	3.90 ± 0.18	0.11 ± 0.01	3.50 ± 0.19	1.88 ± 0.10
0.15	7.53	0.10 ± 0.00	4.87 ± 0.12	4.83 ± 0.12	0.10 ± 0.00	4.78 ± 0.16	1.62 ± 0.06
0.15	10.00	0.10 ± 0.00	6.21 ± 0.23	5.63 ± 0.20	0.10 ± 0.00	6.16 ± 0.22	1.51 ± 0.06
0.20	0.60	0.57 ± 0.04	2.15 ± 0.15	0.83 ± 0.03	0.54 ± 0.03	2.00 ± 0.11	1.05 ± 0.04
0.20	2.55	0.35 ± 0.03	5.69 ± 0.41	1.28 ± 0.05	0.34 ± 0.01	5.51 ± 0.18	1.54 ± 0.08
0.20	5.04	0.29 ± 0.02	9.19 ± 0.67	1.48 ± 0.05	0.28 ± 0.01	9.03 ± 0.24	1.77 ± 0.07
0.20	7.53	0.26 ± 0.02	12.17 ± 0.88	1.56 ± 0.07	0.26 ± 0.01	12.12 ± 0.31	1.87 ± 0.06
0.20	10.00	0.24 ± 0.02	14.83 ± 1.07	1.60 ± 0.09	0.24 ± 0.01	14.89 ± 0.34	1.92 ± 0.06
0.25	0.60	1.68 ± 0.13	6.27 ± 0.48	0.30 ± 0.02	1.67 ± 0.09	6.25 ± 0.35	0.35 ± 0.02
0.25	2.55	0.89 ± 0.07	14.33 ± 1.15	0.53 ± 0.01	0.85 ± 0.04	13.81 ± 0.68	0.58 ± 0.00
0.25	5.04	0.67 ± 0.06	21.10 ± 1.75	0.65 ± 0.00	0.66 ± 0.03	20.79 ± 1.07	0.71 ± 0.01
0.25	7.53	0.56 ± 0.05	26.42 ± 2.21	0.71 ± 0.00	0.56 ± 0.03	26.53 ± 1.36	0.79 ± 0.01
0.25	10.00	0.49 ± 0.04	30.91 ± 2.61	0.75 ± 0.01	0.50 ± 0.03	31.50 ± 1.62	0.84 ± 0.02

Table 5
The effect of concentration of poly(acrylic acid) (C934P) and temperature on the viscoelastic properties of binary systems containing 15% (w/w) poloxamer 407 at five representative frequencies.

Conc. of C934P (% w/w)	Oscillatory frequency (Hz)	Mean (±S.D.) viscoelastic properties at 5 °C			Mean (±S.D.) viscoelastic properties at 37 °C		
		η' (Pa s)	G'' (Pa)	tan δ	η' (Pa s)	G'' (Pa)	tan δ
0.10	0.60	0.08 ± 0.00	0.29 ± 0.00	22.41 ± 0.67	222.72 ± 2.96	833.10 ± 10.99	0.33 ± 0.02
0.10	2.55	0.07 ± 0.00	1.16 ± 0.01	13.09 ± 0.19	46.74 ± 0.96	748.04 ± 15.34	0.23 ± 0.01
0.10	5.04	0.07 ± 0.00	2.21 ± 0.03	11.03 ± 1.01	22.71 ± 0.62	719.84 ± 19.74	0.21 ± 0.01
0.10	7.53	0.07 ± 0.00	3.34 ± 0.06	9.26 ± 0.17	15.02 ± 0.47	710.60 ± 22.27	0.19 ± 0.01
0.10	10.00	0.06 ± 0.00	4.07 ± 0.04	7.55 ± 0.07	11.08 ± 0.37	695.7 ± 23.07	0.18 ± 0.01
0.15	0.60	0.24 ± 0.01	0.89 ± 0.03	0.24 ± 0.01	237.6 ± 13.46	886.74 ± 50.23	0.33 ± 0.01
0.15	2.55	0.18 ± 0.01	2.93 ± 0.10	0.18 ± 0.01	51.04 ± 2.77	816.94 ± 44.38	0.23 ± 0.01
0.15	5.04	0.16 ± 0.01	5.07 ± 0.26	0.16 ± 0.01	25.14 ± 1.34	796.90 ± 42.37	0.21 ± 0.01
0.15	7.53	0.15 ± 0.01	7.31 ± 0.39	0.15 ± 0.01	16.49 ± 0.81	779.96 ± 38.06	0.20 ± 0.01
0.15	10.00	0.15 ± 0.01	9.41 ± 0.39	0.15 ± 0.01	12.28 ± 0.86	771.10 ± 54.01	0.19 ± 0.01
0.20	0.60	0.60 ± 0.06	2.26 ± 0.15	1.40 ± 0.10	237.6 ± 13.46	886.74 ± 50.23	0.33 ± 0.01
0.20	2.55	0.43 ± 0.01	6.93 ± 0.19	1.87 ± 0.10	51.04 ± 2.77	816.94 ± 44.38	0.23 ± 0.01
0.20	5.04	0.36 ± 0.01	11.43 ± 0.27	1.97 ± 0.10	25.14 ± 1.34	796.90 ± 42.37	0.21 ± 0.01
0.20	7.53	0.32 ± 0.01	15.21 ± 0.44	2.00 ± 0.11	16.49 ± 0.81	779.96 ± 38.06	0.20 ± 0.01
0.20	10.00	0.30 ± 0.01	18.53 ± 0.71	2.01 ± 0.13	12.28 ± 0.86	771.10 ± 54.01	0.19 ± 0.01
0.25	0.60	1.55 ± 0.06	5.81 ± 0.21	0.56 ± 0.02	206.86 ± 7.32	773.72 ± 27.36	0.43 ± 0.02
0.25	2.55	0.87 ± 0.05	14.15 ± 0.81	0.88 ± 0.01	52.41 ± 1.05	838.78 ± 16.71	0.33 ± 0.01
0.25	5.04	0.68 ± 0.04	21.44 ± 1.31	1.01 ± 0.01	26.77 ± 0.36	848.56 ± 11.41	0.29 ± 0.01
0.25	7.53	0.58 ± 0.04	27.29 ± 1.72	1.07 ± 0.02	17.68 ± 0.39	836.18 ± 18.56	0.27 ± 0.01
0.25	10.00	0.51 ± 0.03	32.32 ± 2.06	1.11 ± 0.03	13.24 ± 0.19	831.06 ± 12.03	0.25 ± 0.01

Furthermore, the storage moduli (G') of representative binary systems are displayed graphically in Fig. 1. All binary polymeric gels displayed viscoelastic properties that were both temperature and frequency dependent. Increasing the oscillatory frequency significantly decreased the dynamic viscosity and increased the storage modulus of all formulations. The loss modulus of systems containing 10% (w/w) P407 significantly increased as the oscillatory frequency increased; the exceptions being formulations containing 10% (w/w) P407 and 0.20 or 0.25% (w/w) at 37 °C in which the loss modulus significantly decreased as the frequency increased. Whilst the loss modulus of formulations containing 15% (w/w) poloxamer significantly increased as a function of oscillatory frequency, those formulations containing 0.10 and 0.15% (w/w) of C934P displayed significantly decreased loss modulus as the frequency increased at 37 °C. The formulations containing the highest concentration of P407 (20%, w/w) showed significantly increased loss moduli as the oscillatory frequency increased at 5 °C, but conversely this parameter significantly decreased at the higher temperature (37 °C). Increasing the temperature significantly increased the dynamic viscosity and the storage modulus of the binary polymer systems, except those containing 10% (w/w) P407 and either 0.20 or 0.25% (w/w) C934P in which the storage modulus significantly decreased. The loss tangent decreased as the temperature increased.

Importantly, the concentrations of each polymeric component in the binary polymer formulations significantly affected the viscoelastic properties of the various formulations. Increasing the concentration of P407 significantly increased the dynamic viscosity, storage and loss moduli. In contrast, with 15 or 20% (w/w) P407 the dynamic viscosity of the formulations did not significantly increased with the increasing C934P from 0.20 to 0.25% (w/w). The loss tangent was decreased as the concentrations of P407 and C934P were increased. Furthermore, in binary polymer systems containing 10, 15 or 20% (w/w) P407 the storage modulus of all formulations exceeded the loss modulus at 37 °C over the frequency range investigated (0.6–10.0 Hz). At the lower temperature, only those formulations composed of 10% (w/w) P407 and 0.25% C934P

Table 6
The effect of concentration of poly(acrylic acid) (C934P) and temperature on the viscoelastic properties of binary systems containing 20% (w/w) poloxamer 407 at five representative frequencies.

Conc. of C934P (% w/w)	Oscillatory frequency (Hz)	Mean (±S.D.) viscoelastic properties at 5 °C			Mean (±S.D.) viscoelastic properties at 37 °C		
		η' (Pa s)	G'' (Pa)	tan δ	η' (Pa s)	G'' (Pa)	tan δ
0.10	0.60	0.12 ± 0.00	0.45 ± 0.01	18.42 ± 0.60	351.46 ± 4.78	1314.40 ± 17.78	0.10 ± 0.00
0.10	2.55	0.11 ± 0.01	1.78 ± 0.09	12.51 ± 0.52	60.89 ± 1.33	974.66 ± 21.41	0.07 ± 0.00
0.10	5.04	0.10 ± 0.01	3.33 ± 0.16	10.46 ± 0.49	26.86 ± 0.65	851.22 ± 20.54	0.06 ± 0.00
0.10	7.53	0.10 ± 0.00	4.79 ± 0.18	9.20 ± 0.36	16.51 ± 0.44	780.84 ± 21.04	0.05 ± 0.00
0.10	10.00	0.10 ± 0.00	6.23 ± 0.20	8.84 ± 0.88	11.65 ± 0.27	731.16 ± 16.82	0.05 ± 0.00
0.15	0.60	0.29 ± 0.01	1.05 ± 0.09	4.10 ± 0.08	384.18 ± 14.96	1436.60 ± 55.59	0.11 ± 0.01
0.15	2.55	0.23 ± 0.01	3.56 ± 0.38	3.94 ± 0.19	69.64 ± 4.07	1124.40 ± 70.24	0.08 ± 0.00
0.15	5.04	0.21 ± 0.01	6.23 ± 0.50	3.77 ± 0.28	32.37 ± 2.39	1026.92 ± 76.52	0.07 ± 0.00
0.15	7.53	0.19 ± 0.01	8.49 ± 0.49	3.53 ± 0.34	20.82 ± 1.77	984.96 ± 83.63	0.06 ± 0.00
0.15	10.00	0.18 ± 0.01	10.86 ± 0.90	3.51 ± 0.47	15.27 ± 1.43	959.08 ± 89.79	0.06 ± 0.00
0.20	0.60	0.66 ± 0.02	2.45 ± 0.07	2.02 ± 0.05	371.12 ± 10.44	1387.60 ± 38.86	0.11 ± 0.00
0.20	2.55	0.47 ± 0.02	7.63 ± 0.26	2.37 ± 0.05	70.77 ± 2.18	1145.00 ± 35.48	0.08 ± 0.00
0.20	5.04	0.40 ± 0.01	12.75 ± 0.42	2.39 ± 0.07	33.96 ± 1.04	1077.40 ± 33.07	0.07 ± 0.00
0.20	7.53	0.36 ± 0.01	17.24 ± 0.47	2.40 ± 0.08	22.19 ± 0.76	1049.42 ± 35.83	0.07 ± 0.00
0.20	10.00	0.34 ± 0.01	21.32 ± 0.52	2.41 ± 0.08	16.42 ± 0.52	1031.36 ± 32.62	0.07 ± 0.00
0.25	0.60	1.15 ± 0.04	4.30 ± 0.14	1.13 ± 0.04	345.46 ± 12.66	1292.40 ± 47.15	0.11 ± 0.00
0.25	2.55	0.74 ± 0.02	11.96 ± 0.26	1.53 ± 0.04	65.16 ± 1.99	1042.60 ± 31.90	0.08 ± 0.00
0.25	5.04	0.59 ± 0.01	18.88 ± 0.31	1.59 ± 0.03	30.04 ± 0.87	952.04 ± 27.65	0.07 ± 0.00
0.25	7.53	0.52 ± 0.01	24.54 ± 0.34	1.59 ± 0.03	19.06 ± 0.55	901.78 ± 26.07	0.07 ± 0.00
0.25	10.00	0.47 ± 0.01	29.49 ± 0.33	1.58 ± 0.03	13.77 ± 0.42	864.04 ± 26.03	0.06 ± 0.00

Table 7
The observed and calculated values of storage modulus (G') for binary mixtures of poloxamer 407 (P407) and carbopol 934P (C934P) at 5 and 37 °C.

Conc. of P407 (% w/w)	Conc. of C934P (% w/w)	Temperature (°C)	G' observed (Pa)	G' calculated (Pa)	Interaction parameter (Pa)
10.0	0.10	5	0.42 ± 0.00	0.07 ± 0.00	0.35 ± 0.00
10.0	0.10	37	7.19 ± 0.41	15.77 ± 0.02	−8.58 ± 0.41
10.0	0.15	5	1.10 ± 0.00	4.96 ± 0.06	−3.86 ± 0.06
10.0	0.15	37	4.07 ± 0.01	18.63 ± 0.02	−14.56 ± 0.02
10.0	0.20	5	9.29 ± 0.41	52.11 ± 0.54	−42.82 ± 0.63
10.0	0.20	37	7.76 ± 0.31	55.83 ± 1.84	−48.07 ± 1.71
10.0	0.25	5	41.18 ± 3.06	63.14 ± 5.05	−21.96 ± 3.28
10.0	0.25	37	37.67 ± 1.50	87.37 ± 5.54	−49.70 ± 4.07
15.0	0.10	5	0.54 ± 0.00	0.08 ± 0.00	0.46 ± 0.00
15.0	0.10	37	3772.00 ± 94.15	37.88 ± 0.50	3734.12 ± 94.53
15.0	0.15	5	2.57 ± 0.11	4.97 ± 0.05	−2.40 ± 0.08
15.0	0.15	37	4083.60 ± 216.10	40.75 ± 0.49	4042.85 ± 216.47
15.0	0.20	5	9.25 ± 0.48	52.12 ± 0.54	−42.87 ± 0.53
15.0	0.20	37	3477.60 ± 134.97	77.95 ± 1.85	3399.65 ± 136.48
15.0	0.25	5	29.16 ± 1.25	63.15 ± 5.05	−33.99 ± 4.04
15.0	0.25	37	3296.00 ± 201.64	109.48 ± 5.65	3186.52 ± 197.11
20.0	0.10	5	0.71 ± 0.06	0.15 ± 0.01	0.56 ± 0.05
20.0	0.10	37	14412.00 ± 521.70	13696.04 ± 333.44	715.96 ± 23.09
20.0	0.15	5	3.26 ± 0.26	5.05 ± 0.06	−1.79 ± 0.21
20.0	0.15	37	16058.00 ± 1194.93	13698.90 ± 333.43	2359.10 ± 90.68
20.0	0.20	5	8.84 ± 0.11	52.20 ± 0.54	−43.36 ± 0.61
20.0	0.20	37	15532.00 ± 442.35	13736.10 ± 333.23	1795.90 ± 148.58
20.0	0.25	5	18.62 ± 0.49	63.23 ± 5.05	−44.61 ± 4.63
20.0	0.25	37	13974.00 ± 431.72	13767.64 ± 336.26	206.36 ± 15.93

and 15% (w/w) P407 and 0.15% (w/w) C934P displayed a loss tangent less than unity over the frequency range. The values of the observed and calculated storage moduli (at a representative oscillatory frequency of 10.0 Hz) and the calculated interaction parameters for each binary mixture are shown in Table 7, from which two discrete trends may be observed. In general (and with some exceptions), there were (weak) negative interactions observed in all formulations at the lower temperature and, at 37 °C, in formulations composed of 10% (w/w) P407 and C934P (0.10–0.25%, w/w). The extent of the negative interaction generally increased as the concentration of C934P was increased. Conversely, at 37 °C strong positive interactions were apparent in formulations composed of P407 (15 and 20%, w/w) and C934P (0.10–0.25%, w/w). In formulations composed of 15% P407, the greatest positive interactions were observed with 0.20 and 0.25% (w/w) C934P whereas in formulations containing 20% (w/w) P407, the greatest positive interaction was observed in the presence of 0.15% (w/w) C934P.

The sol/gel transition temperatures ($T_{sol/gel}$) of the various formulations are presented in Table 8. As expected monopolymeric systems composed of C934P did not exhibit a sol–gel temperature, whereas those containing P407 (15 and 20%, w/w) exhibited $T_{sol/gel}$ values of 31.53 ± 1.11 and 25.44 ± 0.12 °C, respectively. Binary formulations composed of 10% (w/w) P407 and C934P, irrespective of concentration, did not exhibit a sol/gel temperature. The incorporation of C934P (0.10–0.25%, w/w) did not significantly affect the $T_{sol/gel}$ of systems containing 15% (w/w) poloxamer. Conversely, the sequential increase in concentration of C934P in binary systems containing 20% (w/w) P407 significantly reduced the sol/gel temperature of these systems. Furthermore, Table 8 presents the mechanical and mucoadhesive properties of the formulations under examination. Increasing the concentration of poly(acrylic acid) significantly increased the hardness and compressibility of monopolymeric. Furthermore, increasing the concentration of poloxamer from 10 to 15% (w/w) did not affect the hardness and compressibility of the binary polymeric formulations. The effect of concentration of C934P on the mechanical and mucoadhesive properties of the binary polymeric formulations was dependent on the concentration of poloxamer. Accordingly, increasing the

Table 8
The effects of concentration of poly(acrylic acid (C934P, 0.10–0.25% (w/w)) and poloxamer (P407, 10–20% (w/w)) on the mean (±S.D.) hardness (N), compressibility (N mm), mucoadhesion (N) and sol–gel temperature ($T_{sol/gel}$) of monopolymeric and binary polymeric systems.

Conc. of P407 (%)	Conc. of C934P (%)	Hardness (N)	Compressibility (N mm)	Mucoadhesion (N)	$T_{sol/gel}$ (°C)
0	0.10	0.03 ± 0.00	0.27 ± 0.01	Not Determined	Absent
0	0.15	0.04 ± 0.00	0.28 ± 0.02	Not Determined	Absent
0	0.20	0.04 ± 0.00	0.34 ± 0.03	Not Determined	Absent
0	0.25	0.05 ± 0.00	0.40 ± 0.04	Not Determined	Absent
10	0.00	0.04 ± 0.00	0.29 ± 0.03	Not Determined	Unsuitable
10	0.10	0.04 ± 0.00	0.27 ± 0.02	Unsuitable	Unsuitable
10	0.15	0.04 ± 0.00	0.29 ± 0.02	Unsuitable	Unsuitable
10	0.20	0.04 ± 0.00	0.30 ± 0.03	Unsuitable	Unsuitable
10	0.25	0.04 ± 0.00	0.39 ± 0.01	Unsuitable	Unsuitable
15	0.00	0.04 ± 0.00	0.30 ± 0.02	Not Determined	31.53 ± 1.11
15	0.10	0.07 ± 0.00	0.57 ± 0.06	Unsuitable	34.74 ± 0.38
15	0.15	0.11 ± 0.01	0.91 ± 0.09	Unsuitable	32.50 ± 0.50
15	0.20	0.14 ± 0.01	1.14 ± 0.07	0.27 ± 0.02	32.22 ± 0.86
15	0.25	0.14 ± 0.01	1.10 ± 0.10	0.28 ± 0.02	31.91 ± 0.84
20	0.00	0.40 ± 0.02	3.60 ± 0.13	Not Determined	25.44 ± 0.12
20	0.10	0.52 ± 0.02	4.81 ± 0.16	0.36 ± 0.02	23.44 ± 0.40
20	0.15	0.56 ± 0.02	5.13 ± 0.17	0.38 ± 0.03	23.30 ± 0.05
20	0.20	0.61 ± 0.02	4.78 ± 0.18	0.39 ± 0.03	22.42 ± 0.06
20	0.25	0.75 ± 0.04	6.87 ± 0.24	0.39 ± 0.03	21.84 ± 0.37

concentration of C934P within formulations containing 10% (w/w) P407 did not affect the resultant mechanical properties. Conversely, increasing the concentration of C934P significantly increased the hardness, compressibility and mucoadhesion of binary systems containing 15 and 20% (w/w) poloxamer.

4. Discussion

Formulations designed for use in the oral cavity for the treatment of infection, inflammation or neoplasia should optimally be easy to administer to, and exhibit retention at the site of application. Following administration, these formulations should exhibit elastic properties to optimise retention and offer controlled drug release (Jones et al., 2000; Smart, 2005). Due to the greater required area for treatment of certain oral pathologies, e.g. gingivitis, lichen planus, gel/semi-solid formulations, or in some instances, films/patches are often preferred. For example, Jones et al. (1999) described the physicochemical properties and clinical success of flurbiprofen-containing bioadhesive semi-solids designed for the treatment of gingivitis. Similarly, Mahdi et al. (1996) reported the clinical efficacy of bioadhesive patches for the successful treatment of recurrent aphthous stomatitis. The range of formulations that has been employed to treat periodontal disease, an inflammatory/infective condition in which there is destruction of the supporting structures of the teeth resulting in the formation of a pocket between the gingiva and the tooth, is more extensive (Needleman, 1991; Medlicott et al., 1994). Formulations that have been examined for the treatment of this condition include gels/semi-solids (Jones et al., 2000; Kelly et al., 2004; Okonogi et al., 2004; Feher et al., 2005; Maheshwari et al., 2006), films (Steinberg et al., 1990; Agarwal et al., 1993; Medlicott et al., 1999; Ahuja et al., 2006) and microparticles (Liu et al., 2004; Yue et al., 2004; Chen et al., 2006). Whilst these formulations may be physically retained within the periodontal pocket, the benefits of bioadhesive formulations, i.e. those that interact with the host tissue by secondary bond formation, have been reported (Jones et al., 2000, 2003b; Smart, 2005) and shown to be advantageous (Mahdi et al., 1996; Jones et al., 1999). In addition to the retention of the dosage form at the site of application, two further important parameters to achieve the optimal clinical performance are, the ease of administration to, or adjacent to the affected region and the ability to offer controlled drug release. In the case of gel/semi-solid systems these two requirements present a formulation paradox in that to achieve controlled drug delivery (and indeed optimal retention) a formulation that possesses high elasticity is required however, such formulations will offer resistance to flow, rendering their application to the required site difficult. This presents a serious problem whenever it is required to administer the formulation to the site using a syringe, e.g. for formulations designed for use in the periodontal pocket. Ideally, this scenario may be addressed by the use of formulations whose rheological properties may be significantly modified by, e.g. temperature or moisture. There have been a limited number of studies that have examined this approach, however there are several pendant disadvantages with previous approaches. For example Feher et al. (2005) described a non-aqueous formulation that exhibited highly viscous, lyotropic liquid crystalline behaviour upon contact with aqueous fluid, e.g. crevicular fluid. A similar approach was reported by Okonogi et al. (2004) who described the physicochemical properties of glycerylmonooleate-based formulations that exhibited liquid crystalline behaviour upon contact with aqueous fluid. However, whilst the administration of these systems to the oral cavity and, in particular, to the periodontal pocket is satisfactory, the retention within the periodontal pocket has been reported to be $\leq$24 h (Stoltze, 1995). Therefore, whilst the increased rheological properties of such systems may improve their retention at the site of application, these (and indeed the lack of mucoadhesive properties) are insufficient to ensure long-term retention. Accordingly, in addition to their elastic nature, it is important that such formulations should possess inherent bioadhesive properties. The formulations described in this paper have been designed to address this deficiency.

In the development of topical formulations for the oral cavity, it is important that the flow properties are sufficient to ensure ease of administration. The monopolymeric systems composed of poloxamers were dependent on both concentration and temperature. At low temperatures Newtonian flow was observed at both 5 and 37 °C, indicative of minimal interaction between the polymer chains in solution. In systems composed of 15 or 20% (w/w) poloxamer at the higher temperature, the flow rheograms were pseudoplastic and exhibited greater consistency. These observations are in accordance with the known rheological properties of the Pluronic series (Schmolka, 1972). Consequently, at low concentrations monomolecular polymeric micelles are present in solution, whereas, at higher concentrations, micellar association to produce multi-molecular micelles has been reported, thereby rendering the flow properties of these systems non-Newtonian (Schmolka, 1972). The enhanced rheological structure observed at higher concentrations of poloxamers may be accredited to hydrophobic interactions between adjacent polymer chains following the displacement of bound water (Jones et al., 2003a). Conversely, monopolymeric systems composed of C934P exhibited pseudoplastic flow, independent of temperature and concentration, however, the degree of pseudoplastic behaviour (derived from the rheological exponent) decreased as a function of concentration, due to greater interactions between adjacent polymer chains (Barry and Meyer, 1979). The binary polymeric systems also exhibited pseudoplastic flow, the consistency increasing as a function of increased concentration of each polymeric component. This may be accredited to increased polymer entanglement which, in turn, increased the resistance to deformation (Jones et al., 2000, 2002). With reference to the proposed application of the candidate formulations, it is important to note that, whilst thixotropy was observed in the binary polymeric systems, this was minimal and would not be expected to deleteriously affect formulation retention, particularly when used as the platform for periodontal drug delivery systems. In addition, the consistency of the binary formulations below the sol–gel temperature was low, thereby rendering the systems relatively easy to administer (e.g. through a syringe) (Jones et al., 2000).

The viscoelastic properties of pharmaceutical semi-solids have been reported to affect primary physicochemical properties, e.g. drug release/diffusion (Jones et al., 2000) and mucoadhesion (Tamburic and Craig, 1995; Jones et al., 2000, 2003a). Following removal of the initial shear stress employed during the application of the formulation, the product will undergo rheological recovery and the viscoelastic properties will predominate. In addition, within the biological environment, formulations will be exposed to stresses that will be insufficient to cause deformation and therefore it is pertinent to examine the effects of such stresses on the rheological properties of the formulations. As before the viscoelastic properties of the binary formulations were dependent on the concentration of the polymeric components and temperature. The magnitudes of the viscoelastic properties at 5 °C (G', G'' and, η') were low whereas the loss tangents of the formulations under examination were relatively large; the majority of formulations possessing a loss tangent that was greater than unity. Based on these observations, it may be concluded that the binary formulations were elastoviscous in nature at this lower temperature (Jones et al., 2001). Conversely (and importantly for the proposed application), at 37 °C the formulations containing 15 or 20% (w/w) P407 in addition to C934P were predominantly elastic, exhibiting high G' and η' values and loss tangent values being less than one (Jones et al., 2001). Increasing the concentration of each polymer signif-

icantly increased G', G'' and η'. As a result, the greater elasticity of these formulations would be expected to enhance retention at the site of application and to offer a platform to achieve prolonged, controlled drug release; properties that are beneficial for the proposed application (Andrews et al., 2005; Andrews and Jones, 2006). The differing effects of temperature and polymer concentration on the viscoelastic properties of the formulations may be further highlighted by consideration of the interaction parameters of the various systems (Andrews and Jones, 2006). In this approach rheological synergy has been reported to provide evidence of adhesive interactions between the two polymers (Lenaerts et al., 1987; Jones et al., 2003a). Interestingly, all binary formulations under investigation displayed rheological antagonism at 5 °C in addition to formulations containing 10% (w/w) poloxamer (independent of the concentration of C934P) at 37 °C. Conversely, all binary formulations containing 15 or 20% (w/w) poloxamer exhibited rheological synergy. The disparity in the observed effect of temperature (highlighted as an statistical interaction within the ANOVA) provides an insight as to the effect of the state of P407 on the subsequent physical interaction with poly(acrylic acid). At 5 °C, the poloxamer chains will be present in a range of states depending on the concentration of polymer. Therefore, as the concentration is raised from 10–15 to 20% (w/w), the poloxamer chains will be initially present as monomolecular micelles, in which the hydrophobic poly(oxypropylene) segments are protected from the aqueous phase by the hydrophilic poly(oxyethylene) segments. As the concentration of poloxamer is increased, intermicelle aggregation increasingly occurs, which, in turn, results in an increase in the viscoelastic properties (G', G'' and η'). Poly(acrylic acid) may interact with P407 through hydrogen bonding and other secondary interactions, however, the observed rheological antagonism at 5 °C infers that the rheological properties of P407 were compromised by C934P. In general increasing the concentration of poly(acrylic acid) increased the rheological antagonism in systems containing 10% (w/w) P407. This may be accredited to the ability of C934P to interfere with monomicelle or multimicelle formation, which in turn reduced the storage modulus of the candidate formulations. As the concentration of poloxamer increased from 15 to 20% (w/w), the modulus of the formulations increased however, the extent of the rheological antagonism decreased. This may be explained by the increased molar ratio of P407 to C934P and therefore, whilst the number of interactions between the two polymers has remained constant, the number of free poloxamer molecules that are free to self-associate has increased. At 37 °C rheological antagonism was observed for all binary mixtures containing 10% (w/w) P407 and the moduli of the formulations were not affected by the temperature increase. Therefore, the concentration of poloxamer was both insufficient to undergo the sol/gel transition whereas the observed rheological antagonism may be explained by the ability of poly(acrylic acid) to interfere with micellisation of the poloxamer molecules. Conversely, pronounced rheological synergy was observed in binary systems composed of 15 and 20% (w/w) P407. Furthermore, whilst the modulus of binary systems composed of 15% (w/w) P407 were significantly lower than those composed of 20% (w/w) poloxamer, the magnitude of rheological synergy associated with the former systems was greater. Therefore, it may be suggested that the effect of C934P on the modulus of P407 is dependent on the state of association of the poloxamer molecule. It may be suggested that the degree of intermicelle aggregation (multimicelle formation) is lower in the binary systems composed of 15% (w/w) P407 and therefore, in binary systems composed of 20% (w/w), an intermicellar network was present that was more resistant to mechanical deformation. Whilst in both systems, the increased temperature of the system facilitated hydrophobic bonding between the poly(oxypropylene) segments of adjacent micelles, the density of these interactions was lower in the binary systems containing 15% (w/w) P407. However, the greater modulus of P407 (15%, w/w) in the presence of poly(acrylic acid) (in comparison to the comparator system devoid of C934P) may be suggested to be due to the facilitation of intermicellar interactions due to the ability of this polymer to interact with the poly(oxyethylene) regions of adjacent micelles and, in so doing, increase cross-link density. Furthermore, the observed effects may be due in part to desolvation of poloxamers induced by poly(acrylic acid), a strong electrolyte. This is consistent with previous reports in which there was an increase in poloxamer viscosity and elasticity in the presence of strong electrolytes (Jones et al., 2003a). Interestingly, there was no overall effect of C934P on the sol/gel transition temperature of P407 within the binary mixtures, reflecting the interplay between the two mechanisms of interaction. Desolvation of poloxamers has been reported to lower $T_{gel/sol}$ whereas, network formation between poloxamer and C934P would be expected to elevate the sol–gel transition temperature in a fashion similar to the effect of polymer crosslinking on the glass transition temperature. As previously stated, the rheological synergy observed between P407 (20%, w/w) and poly(acrylic acid) was significant but lesser than that observed with P407 (15%, w/w), however the overall modulus of the former system was greater. In this system, the higher concentration of P407 will ensure that the aggregation number of the micelles is greater, leading to high and low storage modulus and loss tangent values, respectively. Under these conditions poly(acrylic acid) may serve to enhance the network structure through secondary bond formation with P407, however, the hydrophobic interactions between the poloxamer chains are of greater significance. In this scenario, the inter-polymer bonds are not as significant to the overall modulus of the network as those between adjacent poloxamer micelles. This is confirmed by the sequential decrease in $T_{sol/gel}$ associated with an increase in the concentration of poly(acrylic acid).

As the formulations under investigate will be applied to the host surface, either following expression from a tube or *via* a syringe, their flow properties under compressional stresses is a important parameter in the proposed clinical application. The effects of increasing concentration of each polymeric component on the hardness and compressibility may be explained by increased polymer entanglement. These observations are in accordance with the results concerning polymer effects on the viscoelastic and flow properties of the formulations. Of relevance to the proposed application is the low hardness and compressibility of the formulations. The compressional flow properties were measured at 20 ± 0.5 °C and therefore the hardness/compressibility of formulations composed of 20% (w/w) P407 and 0.20/0.25% (w/w) C934P may reflect the initial stages of the sol–gel transition. Even under these circumstances the compressional flow properties of all formulations were appropriate and will ensure ease of administration to the proposed site. It is worthwhile to reflect that the hardness and compressibility of the formulations were markedly lower than those for formulations that were successfully clinically evaluated (Jones et al., 2000). One of the important design criteria for the drug delivery platforms is their ability to exhibit mucoadhesion. Whilst there have been several models used to assess the mucoadhesive properties of formulations, the method used in this study has been used to successfully identify mucoadhesive formulations and to quantify their relative mucoadhesive properties (Jones et al., 1997a,b, 2000). Using this model, formulations containing 20% P407 and C934P (01.0–0.25%, w/w) and 15% P407 and 0.20 and 0.25% (w/w) C934P possessed significant mucoadhesive properties. Interestingly, at each poloxamer concentration, increasing the concentration of C934P did not significantly increase the force required to break the mucoadhesive bond. Furthermore, the mucoadhesive properties of formulations containing 20% (w/w) P407 were greater than those containing lower concentrations of this polymer. These observations infer that the mucoadhesive properties of the for-

mulations are due to an interplay between the ability of C934P, the mucoadhesive component, to diffuse into and interact with mucin and the effect of the rheological structure of the formulation at the interface between the formulation and mucin. The importance of formulation elasticity in the resultant mucoadhesive behaviour has been previously reported (Tamburic and Craig, 1995; Jones et al., 2000). Of great interest to the potential clinical utility of these formulations is the magnitude of the mucoadhesion exhibited. The mucoadhesive properties of the current formulations (containing 20%, w/w P407 and C934P) are statistically similar to those described in a previous study (Jones et al., 2000) in which prolonged retention within the periodontal pocket was clinically observed. Accordingly the formulation platform described in this formulation offers particular promise.

5. Conclusions

This study described the thermorheological, mechanical and mucoadhesive properties of thermoresponsive mucoadhesive properties of binary polymeric platforms composed of poloxamer and poly(acrylic acid). The viscoelastic, flow rheological, compressional and mucoadhesive properties of the binary systems were affected by the concentration of each component and temperature. Formulations containing 15 and 20% (w/w) poloxamer and poly(acrylic acid) exhibited a sol–gel temperature, which directly affected the resultant physicochemical properties. Importantly the flow and compressional properties of the formulations were minimal below the sol–gel temperature, properties that will facilitate application to the required site within the oral cavity. Conversely, above the sol–gel transition temperature, the formulations exhibited wide ranges of viscoelastic, mechanical and mucoadhesive properties that were manipulated by changing the concentrations of the polymeric components. The high elasticity and mucoadhesion would render formulations composed of 15 and 20% (w/w) P407 and C934P potentially useful as platforms for controlled topical drug delivery within the oral cavity.

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