Rheological Characterization of Bioadhesive Binary Polymeric Systems Designed as Platforms for Drug Delivery Implants

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This study describes the formulation and characterization of binary interactive polymeric systems, designed as platforms for improved drug delivery to mucosal sites. Binary interactive systems were manufactured containing hydroxyethylcellulose (HEC; 1−5% w/w) and polycarbophil (PC; 1−5% w/w) at pH 7, and their rheological (flow and dynamic), mechanical, and mucoadhesive properties were characterized, both before and after dilution with phosphate buffered saline (designed to mimic dilution by biological fluids). Physical interactions between HEC and PC were confirmed by the observed rheological synergy. Within the binary interactive systems increasing polymer concentration increased the storage modulus (G'), loss modulus (G''), dynamic viscosity (η'), hardness, compressibility, consistency, and mucoadhesion yet decreased the loss tangent. This was attributed to enhanced entanglements and interactions between adjacent polymer chains. Dilution with PBS altered the above properties; however, the binary interactive systems, particularly those containing higher concentrations of HEC, still exhibited predominantly elastic properties (high G', low tan δ). In light of this, it is suggested that the rheological and mucoadhesive properties of binary interactive systems composed of HEC (5% w/w) and PC (1−3% w/w) offered particular promise as platforms for topical mucosal drug delivery systems.

1. Introduction

It is commonly accepted that the treatment of local diseases, e.g., infection or inflammation, is most effectively performed by the topical delivery of the required therapeutic agent to the target tissue.[1] Examples of this include the treatment of periodontal disease,[1] gingivitis,[2] oral cancer,[3] cervical intracellular neoplasia,[4] oral and vulval/vaginal lichen planus,[5,6] and the prevention of sexually transmitted diseases (including HIV/AIDS).[7] The formulation of topical drug delivery systems for administration to and retention at the appropriate site of application, e.g., the oral cavity or vagina, requires knowledge of the structural (equilibrium) rheological properties (in light of their effects on drug diffusion) and flow rheological properties (to ensure ease of administration and spreading onto the site of application), whereas to ensure prolonged efficacy, the dosage form should interact with and hence be retained at the site of application for extended periods.[1,8,9] The latter concern is particularly relevant as in the various mucosal-lined body cavities (e.g., the oral-pharyngeal cavities, the rectum, and the vagina) the physiological conditions imposed by the protective mechanisms at these sites limits the efficacy of topical formulations. The self-cleaning mechanisms, in addition to normal physiological functions (e.g., swallowing or chewing within the oral cavity) effectively limit the contact between the administered dosage form and the topical mucosa.[9] As a means of overcoming the problem of poor retention, mucoadhesive drug delivery systems, formulations that interact with and are subsequently retained at the applied site for an extended period and provide controlled drug delivery for the duration of retention, have received considerable attention.[10−13] The role of the structural (equilibrium) rheological properties on the resultant retention at the site of application have been reported in previous studies, thereby further highlighting the overall importance of product rheology on the performance of implantable pharmaceutical systems.[1,14,15]

Polymers that have been utilized to formulate mucoadhesive topical implants include poly(acrylic acid), poly(vinylpyrrolidone), sodium carboxymethylcellulose, and hydroxypropylcellulose.[10,16−18] Although these polymers have proven to be useful in enhancing product retention,[1,2,18] there are inherent difficulties in the formulation of mono-polymeric gel systems (using for example the aforementioned polymers) that are both mucoadhesive and possess appropriate rheological properties to facilitate administration into and spreading onto the host substrate and, following administration, regain rheological structure to offer controlled drug delivery and promote retention at the site of application. In addition, one of the major disadvantages of implantable gel/semisolid drug delivery systems for topical application to the oral cavity, rectum, or vagina is the destruction of the rheological properties of the formulation in vivo following dilution with the associated body fluid, which ultimately leads to rapid leakage and hence poor retention of the formulation and improper control of drug release.

Given therefore that the rheological properties of gel systems are pertinent to their clinical success, there has been an increased interest in the formulation of rheologically structured gels for pharmaceutical applications. Formulations designed as drug delivery implants are subjected to a wide range of shearing stresses, which may be within destructive and nondestructive regimes. Consequently, the effects on the gel/semisolid structure may vary considerably. In vivo shear rates experienced by gel systems within the vagina are estimated to range from 0.1 s^{-1} during passive seepage between epithelial surfaces to 100 s^{-1} during sexual intercourse. Moreover, it has been reported that in addition to the high stresses associated with mastication, formulations implanted into the oral cavity will be exposed to nondestructive oscillatory stresses (>0.5 Hz). Therefore, the

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characterization and hence selection of gels/semisolids as topical implantable systems should involve a comprehensive rheological evaluation, which would be expected to include both transient and destructive testing methods.

Despite the importance of rheological properties to product performance, there have been comparatively few attempts to formulate systems possessing enhanced rheological structure in addition to mucoadhesive ability. Therefore, in this study, we have addressed this discrepancy using binary interactive polymer mixtures in which rheological synergy may be achieved due to the interactions between the chosen polymer components[19] Candidate polymeric binary gel systems, containing hydroxyethylcellulose (HEC) and polycarbophil (PC), chosen in light of their propensity to form interactive mixtures, have been formulated and their rheological, mechanical, and mucoadhesive properties determined. It is proposed that, by understanding these properties, binary polymeric systems may be developed as novel drug delivery platforms for use as implantable drug delivery systems, which possess improved physicochemical properties. Furthermore, this study uniquely describes the effect of dilution on the rheological properties of these systems, thereby providing an indication of the possible persistence of the properties in the clinical scenario.

2. Materials and Methods

Materials. Hydroxyethylcellulose (Natrosol 250 HHX) was a gift from Aqualon Ltd. (Warrington, England). Polycarbophil (Noveon AA1) was kindly provided by B. F. Goodrich (Cleveland, OH). Crude porcine mucin was purchased from Sigma Chemical Company (Poole, England). All other chemicals were purchased from BDH Laboratory supplies and were of AnalaR grade, or equivalent quality.

Preparation of Gel Systems. Primary polymeric systems containing HEC (3 and 5% w/w) and PC (1, 3, and 5% w/w) were prepared by initially introducing the polymer to a vortex, which was generated by stirring the required amount of isotonic phosphate buffered saline (PBS; pH 7.0) at high speed (2000 rpm). Formulations were then transferred into amber ointment jars and stored at 4 °C for 24 h to ensure complete wetting. Binary polymeric systems containing HEC (3 and 5% w/w) and PC (1, 3, and 5% w/w) were prepared by initially formulating the primary HEC gel in isotonic PBS (pH 7) and then adding the required amount of PC powder with thorough mixing. Samples were subsequently stored at 4 °C for 24 h to ensure complete mixing.

In Vitro Gel Dilution. The candidate gel systems will experience dilution in vivo, and accordingly, it is important to characterize this effect by dilution of the prepared gel systems with isotonic PBS (pH 7.0). In this, a defined mass (2 g) of gel was thoroughly mixed with 0.9 mL of PBS, and the mucoadhesive, rheological (flow and dynamic), and mechanical (textural) properties of the diluted gel systems were subsequently analyzed as described below. The dilution ratio was selected to represent that normally encountered in the body, e.g., the vagina, following implantation of the drug delivery system.[20]

Dynamic (Oscillatory) Rheological Analysis. Dynamic (oscillatory) rheological analysis of all formulations (both undiluted and diluted) was performed using a Carri-Med CSL^2-100 controlled stress rheometer (T. A. Instruments, Surrey, England) at 20.0 ± 0.1 °C using a 2, 4, or 6 cm parallel plate geometry (dependent on sample consistency) and a sample gap of 1 mm.[15,19] Samples of each formulation were applied to the lower plate of the rheometer and allowed to equilibrate for at least 30 min prior to analysis. Initially, the linear viscoelastic region for each system was identified following a torque sweep from 0.1 to 100 Pa at frequencies of 0.01 and 1.0 Hz as the region where stress was directly proportional to strain, and the storage modulus (G') remained constant. All frequency sweep analyses were investigated over the frequency range of 0.01−1.0 Hz following application of a constant strain (0.0065 for primary HEC and binary samples and 0.02 for primary PC samples). The storage modulus (G'), loss modulus (G''), dynamic viscosity (η'), and loss tangent (tan δ) were then determined using Rheology Solutions software provided by T. A. Instruments. In each case, the dynamic rheological properties of six replicates were determined.

Calculation of Interaction Parameter. The interaction between HEC and PC in the binary systems was determined by calculating the rheological synergy as previously reported.[21] This method assesses the difference between the actual dynamic modulus of the mixture and the theoretical (additive) value of the modulus. Calculation of the interaction parameter for HEC/PC binary mixtures was determined using the storage modulus values at an oscillatory frequency of 1 Hz as follows:

$$\Delta G' = G'_{\mathrm{mix(HEC/PC)}} - (G'_{\mathrm{HEC}} + G'_{\mathrm{PC}}) \quad (1)$$

Flow Rheology. Six replicate flow rheograms of each formulation were determined at 20 ± 0.1 °C, using a Carri-Med CSL^2-100 rotational rheometer in continuous shear analysis mode using a parallel plate geometry and a fixed gap of 1 mm as described previously by the authors.[22,23] The sample geometry was selected according to the consistency of the formulations. Modeling of the flow properties of the various formulations was performed using the Power Law (Oswald-de-Waele)[24] (eq 2), Sisko[24] (eq 3), and Cross[25] (eq 4) models, as follows:

$$\sigma = \mathrm{k}\dot{\gamma}^n \quad (2)$$

where σ is the shearing stress, $\dot{\gamma}$ is the rate of shear, k is the consistency, and n is the pseudoplastic index

$$\eta = \eta_\infty + k\,\dot{\gamma}^{n-1} \quad (3)$$

where η is the viscosity, $\dot{\gamma}$ is the rate of shear, k is the consistency, and η_∞ is the infinite shear viscosity

$$\frac{\eta_0 - \eta}{\eta - \eta_\infty} = (k\,\dot{\gamma})^m \quad (4)$$

where η is the viscosity, η_0 is the zero rate viscosity, η_∞ is the infinite shear viscosity, k is the consistency, $\dot{\gamma}$ is the shear rate, and m is the slope of the curve at the inflection point

Examination of the Mechanical (Compressional Flow) Properties. The mechanical (compressional flow) properties (hardness and compressibility) of all formulations were determined using a TA-XT2 Texture Analyzer (Stable Micro Systems, Surrey, England) in compression mode as previously described.[22,23] In this, formulations (16 g) were packed into McCartney bottles and centrifuged to remove entrapped air. An analytical polycarbonate probe (1 cm diameter) was compressed into each sample at a defined rate (10 mm s^{-1}) and to a defined depth (15 mm). Six replicate analyses of each sample were performed at ambient temperature, and from the resultant force−distance plot, the hardness and compressibilities were derived, as follows:

(a) Hardness: the maximum resistance to probe compression (defined as the peak value in the force−distance plot)

(b) Compressibility: the work done in compressing the probe (defined as the area under the force−distance plot)

In Vitro Assessment of Mucoadhesion. The mucoadhesive properties of primary and binary gels were evaluated using a TA-XT2 Texture Analyzer and a previously described mucin disk test[1]. In brief, mucin disks (13 mm diameter), prepared by compression of crude porcine mucin (10 tonnes, 30 s), were attached onto the lower facer of a horizontal probe and immersed in a mucin solution (5% w/w) for 30 s. The mucin disk was then allowed to contact the formulations under examination and a downward force (0.1 N) applied for 10 min. The probe was then elevated at 1 mm s^{-1} and the mucoadhesion of each formulation determined as the force of detachment. In total the mucoadhesive properties of six replicates of each formulation were determined.

Statistical Analysis. The effect of polymer concentration and polymer type on the mucoadhesive bond strength, viscoelastic properties

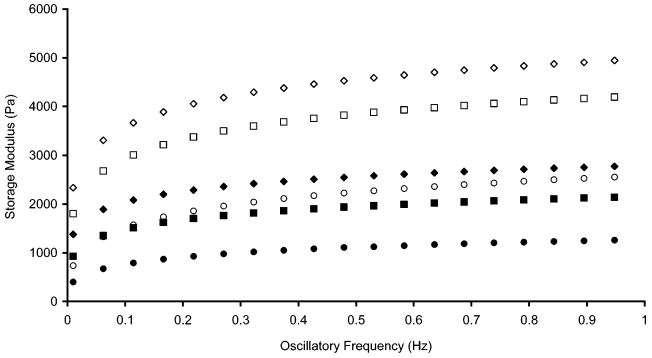

Figure 1. Frequency dependence of the storage modulus (G') for aqueous binary interactive systems composed of HEC (3% w/w closed symbols or 5% w/w open symbols) and PC (1% w/w circles, 3% w/w squares and 5% w/w diamonds). Standard deviations have been omitted for clarity, however, and in all cases, the coefficient of variance was less than 5%.

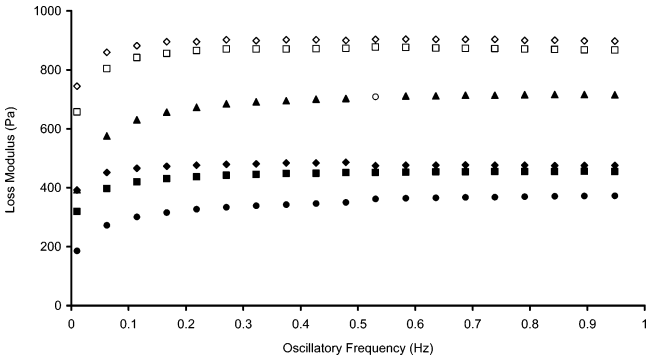

Figure 2. Frequency dependence of the loss modulus (G'') for aqueous binary interactive systems composed of HEC (3% w/w closed symbols or 5% w/w open symbols) and PC (1% w/w circles, 3% w/w squares and 5% w/w diamonds). Standard deviations have been omitted for clarity however, and in all cases; the coefficient of variance was less than 4%.

(G', G'', tan δ, and η') at defined representative frequencies (0.06, 0.27, 0.53, 0.74, and 1.0 Hz) and mechanical (compressional flow) properties (hardness and compressibility) were statistically compared using a two-way ANOVA (Statview, Abacus Concepts, CA). Furthermore, statistical comparison of the modulus of binary mixtures and the theoretical modulus following addition of the individual moduli at five defined frequencies (0.06, 0.27, 0.53, 0.74, and 1.0 Hz) were performed using an unpaired Students' *t*-test. Evaluation of the most appropriate flow model was performed by statistical comparison of the standard errors associated with each formulation using a one-way ANOVA; the model associated with the lowest standard error defined as the most appropriate. In all cases, post-hoc comparisons of the means of individual groups (following the ANOVA) were performed using Tukey's Honestly Significant Difference test. A significance level of $p < 0.05$ was accepted to denote significance in all cases.[26]

3. Results

The variation in the storage and loss modulus of all formulations as a function of oscillatory frequency is graphically depicted in Figures 1 and 2, respectively, whereas the loss tangent and the dynamic viscosity at five selected oscillatory frequencies are displayed in Table 1. The viscoelastic properties of the polymer gels were significantly influenced by the concentrations of both HEC and PC and the oscillatory frequency. Typically, increasing the concentration of HEC and PC and the oscillatory frequency increased the storage (G') and loss (G'') moduli. However, the relative increases in these moduli as a function of frequency were small. The loss tangent decreased as a function of increasing the concentration of PC and HEC (from 1 to 3% w/w) and oscillatory frequency whereas increasing the concentration of HEC from 3 to 5% w/w had no effect on this parameter. The dynamic viscosity was significantly decreased as a function of increasing oscillatory frequency and increased as a function of increasing HEC and PC concentrations.

Table 1. Effect of Polymer Concentration on the Viscoelastic Properties (tan δ and η') of Binary Gel Systems at Five Representative Frequencies

formulation (%w/w) HEC/PC	frequency (Hz)	mean (± s.d.) tan δ	mean (± s.d.) η' (Pa.s)
3/1	0.06	0.41 ± 0.02	700.3 ± 27.3
3/1	0.27	0.34 ± 0.01	196.7 ± 7.9
3/1	0.53	0.32 ± 0.00	110.4 ± 4.7
3/1	0.74	0.31 ± 0.00	80.6 ± 3.7
3/1	1.00	0.29 ± 0.00	60.4 ± 2.8
3/3	0.06	0.29 ± 0.01	1018.3 ± 16.8
3/3	0.27	0.25 ± 0.00	260.0 ± 5.4
3/3	0.53	0.23 ± 0.00	135.6 ± 3.4
3/3	0.74	0.22 ± 0.00	97.9 ± 2.4
3/3	1.00	0.21 ± 0.00	72.3 ± 2.0
3/5	0.06	0.24 ± 0.01	1158.0 ± 30.5
3/5	0.27	0.21 ± 0.00	282.0 ± 8.1
3/5	0.53	0.19 ± 0.00	142.5 ± 4.8
3/5	0.74	0.18 ± 0.00	102.7 ± 4.0
3/5	1.00	0.17 ± 0.00	75.77 ± 3.01
5/1	0.06	0.43 ± 0.01	1475.0 ± 79.2
5/1	0.27	0.35 ± 0.01	402.7 ± 20.7
5/1	0.53	0.31 ± 0.01	212.5 ± 12.4
5/1	0.74	0.29 ± 0.01	153.7 ± 9.0
5/1	1.00	0.28 ± 0.00	113.9 ± 7.2
5/3	0.06	0.30 ± 0.02	2092.7 ± 133.0
5/3	0.27	0.25 ± 0.01	521.1 ± 33.7
5/3	0.53	0.23 ± 0.00	268.4 ± 13.2
5/3	0.74	0.21 ± 0.00	191.6 ± 9.7
5/3	1.00	0.21 ± 0.00	140.0 ± 7.9
5/5	0.06	0.26 ± 0.01	2202.7 ± 114.1
5/5	0.27	0.22 ± 0.01	530.7 ± 24.1
5/5	0.53	0.18 ± 0.01	271.0 ± 15.1
5/5	0.74	0.19 ± 0.01	194.6 ± 10.6
5/5	1.00	0.18 ± 0.00	142.6 ± 7.7

The frequency dependence of the storage moduli was fitted to a general power law model using a double logarithmic transformation in conjunction with least squares linear regression, as follows (eq 5):

$$G_f = kf^n \tag{5}$$

where G_f refers to the storage modulus (G) at the specified frequency, k is the oscillatory consistency, f is the oscillatory frequency, and n is the oscillatory exponent.

The data obtained from this analysis is shown in Table 2 for all binary polymer systems and for the comparator single component systems. Significant decreases in the oscillatory exponent (n) were observed as the concentration of PC was increased within the binary mixtures whereas increasing the concentration of HEC (3−5%vw/w) did not significantly affect this parameter. Furthermore increasing the concentration of HEC and PC significantly increased the oscillatory consistency (k), a measure of the storage modulus at a frequency of 1 Hz. In mono-polymeric systems increasing the concentration of PC

Table 2. Frequency Dependence of the Storage Modulus Obtained for Mono and Binary Polymeric Gel Systems, Modeled Using a Power Law Model[a]

formulation (w/w)	mean (± s.d.) oscillatory consistency (Pa)	mean (± s.d.) oscillatory exponent (*n*)
3% HEC 1% PC	1271.7 ± 51.6	0.24 ± 0.01
3% HEC 3% PC	2154.0 ± 65.0	0.18 ± 0.00
3% HEC 5% PC	2788.3 ± 150.7	0.15 ± 0.00
5% HEC 1% PC	2578.0 ± 158.4	0.26 ± 0.01
5% HEC 3% PC	4222.3 ± 118.0	0.18 ± 0.01
5% HEC 5% PC	4974.3 ± 347.5	0.16 ± 0.01
3% HEC	393.0 ± 9.9	0.51 ± 0.01
5% HEC	1388.3 ± 11.9	0.38 ± 0.01
1% PC	42.0 ± 0.3	0.04 ± 0.00
3% PC	241.3 ± 14.8	0.03 ± 0.00
5% PC	547.2 ± 12.7	0.03 ± 0.00

[a] Modeled using the power law relationship $G_f = kf^n$, where G_f refers to the storage modulus (G) at the specified frequency, k is the oscillatory consistency (the storage modulus at 1 Hz), f is the oscillatory frequency, and n is the oscillatory exponent.

Table 3. Observed and Calculated Values of the Mean (±Standard Deviation) Storage Modulus for Binary Interactive Mixtures of Hydroxyethylcellulose (HEC) and Polycarbophil (PC)

formulation	G' (Pa)[a]	interaction parameter (Pa)
3% HEC 1% PC (observed)	1271.7 ± 51.6	836.6 ± 41.6
3% HEC 3% PC (observed)	2154.0 ± 65.0	1519.8 ± 80.9
3% HEC 5% PC (observed)	2788.3 ± 150.7	1848.1 ± 51.9
5% HEC 1% PC (observed)	2578.0 ± 158.4	1147.6 ± 63.6
5% HEC 3% PC (observed)	4222.3 ± 118.0	2592.8 ± 66.9
5% HEC 5% PC (observed)	4974.3 ± 347.5	3038.9 ± 77.4
3% HEC 1% PC (calculated)	435.0 ± 10.0	
3% HEC 3% PC (calculated)	634.3 ± 18.5	
3% HEC 5% PC (calculated)	940.2 ± 17.2	
5% HEC 1% PC (calculated)	1433.4 ± 10.6	
5% HEC 3% PC (calculated)	1629.6 ± 21.4	
5% HEC 5% PC (calculated)	1935.5 ± 19.9	

[a] G' determined at an oscillatory frequency of 1 Hz.

significantly increased k, whereas the oscillatory exponent was unchanged. Gel systems in which only HEC was present however displayed significant increases in the k constant and significant decreases in the oscillatory exponent as a function of increasing HEC concentration.

The values of the observed and calculated storage moduli (at a representative oscillatory frequency of 1 Hz) and the calculated interaction parameters for each binary mixture are shown in Table 3. Characteristically for both the calculated and observed storage modulus values, increasing the concentration of HEC and PC within the binary mixture significantly increased the storage modulus at 1 Hz. Furthermore similar trends were apparent for the interaction parameters. Increasing the concentration of both HEC and PC significantly increased the interaction parameter such that the greatest interaction parameter was displayed by the binary mixture containing 5% w/w HEC and 5% w/w PC (3038.85 ± 77.35 Pa), whereas the lowest interaction parameter was displayed by the system containing 3% w/w HEC and 1% w/w PC (836.63 ± 41.59 Pa). Statistical analysis of the interaction between the two polymers was additionally examined at four other frequencies (0.06, 0.27, 0.53, 0.74, and 1.0 Hz) and, importantly, although the observed moduli changed, the observed trends were similar to those observed at 1 Hz (Table 3).

All of the binary interactive systems were pseudoplastic with limited thixotropy. Figure 3 presents representative flow rheograms for the mono-polymeric gels (Figure 3, panels a and b) and binary interactive systems (Figure 3, panels c and d). The decreases in the non-Newtonian viscosity as a function of increasing shear rate were most appropriately mathematically modeled using a Power law (Oswald−de Waele) model, from which the consistency (k) and pseudoplastic index (n) were determined (Table 4). As may be observed, increasing the concentrations of HEC and PC within the binary mixtures significantly increased the gel consistency (k). Increasing the concentrations of HEC (3−5% w/w) had no effect on the pseudoplastic index, whereas increasing the concentration of PC within the binary mixtures from 1 to 3% w/w but not from 3 to 5% significantly decreased the pseudoplastic index. Increasing the concentration of either PC or HEC within the mono-polymeric gels significantly enhanced the consistency and reduced the pseudoplastic index.

The mechanical and mucoadhesive properties of all formulations are presented in Table 5. Formulations containing 1, 3, and 5% w/w PC were unsuitable for mechanical analysis due to the resistance to compressional flow being below the limit of detection of the apparatus. The formulations examined within this study displayed a wide range of mechanical and mucoadhesive properties that were significantly (and sequentially) affected by changes in the polymer concentration. For example, increasing the concentration of HEC (3 to 5%w/w) within single component systems and increasing the concentration of HEC and PC within the binary systems significantly increased formulation hardness, compressibility, and mucoadhesion.

The effects of dilution of the various gel systems under investigation with PBS on their mechanical and mucoadhesive properties are presented in Table 5, whereas the ratios of the storage moduli of binary interactive systems to that of their diluted counterparts across the frequency range investigated (0.01−1.00 Hz) are illustrated in Figure 4. As may be observed, the ratio of the storage modulus of the binary gels to the diluted counterparts decreased as functions of both oscillatory frequency and polymer concentration. Accordingly the binary formulation containing HEC and PC (both 5% w/w) exhibited the lowest ratio of gel to diluted gel (and therefore the greatest rheological structures following dilution), whereas the greatest ratio was observed for the system containing 3% w/w HEC and 1% w/w PC. Similarly, the mechanical and mucoadhesive properties of the various gel systems were significantly decreased by dilution. Moreover, the formulation hardness, compressibility and mucoadhesion significantly increased as the concentrations of HEC and PC were raised, even following dilution.

4. Discussion

The successful delivery of therapeutic agents from topical systems is compromised by the poor retention of conventional formulations at the site of implantation, due to removal by physiological and mechanical processes, e.g., chewing, swallowing, and digestion of food) and by dilution with body fluids, e.g., saliva.[15] The retention time of implantable drug delivery systems may be enhanced by the use of mucoadhesive polymers.[1,2,27] However, although mucoadhesive polymers, such as polycarbophil, significantly increase epithelial adhesion, their rheological properties are frequently insufficient to offer optimal mucoadhesion and hence clinical performance. Optimally, such formulations should be highly elastic (large G', low loss modulus), particularly following dilution with body fluids, as

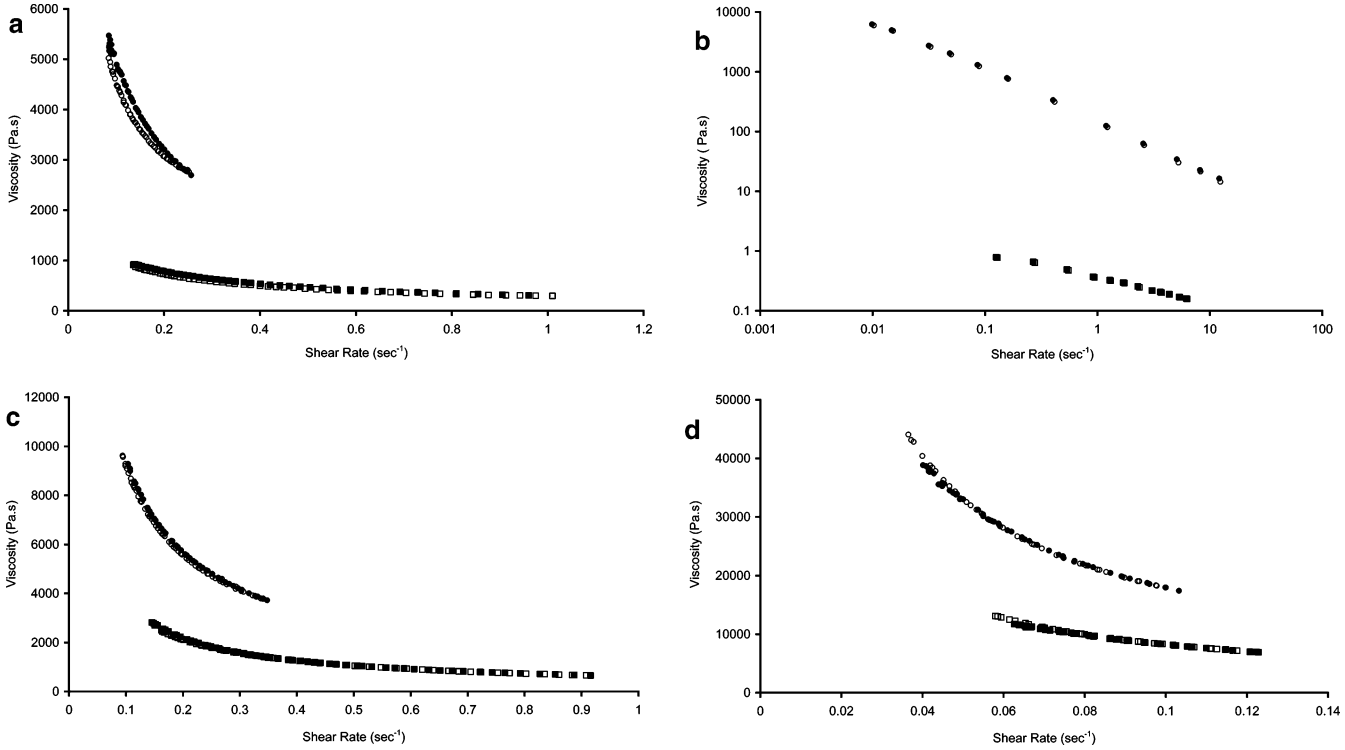

Figure 3. (a) Flow rheograms of gels composed of 3% w/w (squares) or 5% w/w (circles) HEC. Each curve has been calculated from the average of five experiments, and in all cases, the coefficient of variance was less than 5%. Closed symbols refer to the up curve, whereas open symbols denote the down curve. (b) Flow rheograms of gels composed of 1% w/w (squares) and 5% w/w (circles) PC. Each curve has been calculated from the average of five experiments, and in all cases, the coefficient of variance was less than 3%. Closed symbols refer to the up curve whereas open symbols denote the down curve. (c) Flow rheograms illustrating the limited thixotropy of 1% w/w PC gels containing 3 and 5% w/w HEC (squares and circles, respectively). Each curve has been calculated from the average of five experiments, and in all cases, the coefficient of variance was less than 4%. Closed symbols refer to the up curve whereas open symbols denote the down curve. (d) Flow rheograms of 5% w/w PC gels containing 3 and 5% w/w HEC (squares and circles, respectively). Each curve has been calculated from the average of five experiments, and in all cases, the coefficient of variance was less than 4%. Closed symbols refer to the up curve whereas open symbols denote the down curve.

Table 4. Oswald−de Waele Parameters for Formulations Composed of Hydroxyethylcellulose (HEC), Polycarbophil (PC), and Their Binary Interactive Mixtures

formulation	mean (± s.d.) consistency (k) (Pa.s^n)	mean (± s.d.) pseudoplastic index (n)
1% PC	0.4 ± 0.0	0.53 ± 0.02
3% PC	48.3 ± 3.1	0.15 ± 0.01
5% PC	146.0 ± 0.6	0.11 ± 0.00
3% HEC	306.0 ± 2.7	0.40 ± 0.01
5% HEC	1108.1 ± 42.5	0.34 ± 0.02
3% HEC 1% PC	609.2 ± 3.9	0.21 ± 0.01
3% HEC 3% PC	993.1 ± 25.8	0.15 ± 0.01
3% HEC 5% PC	1237.0 ± 135.1	0.14 ± 0.02
5% HEC 1% PC	1637.3 ± 88.8	0.24 ± 0.04
5% HEC 3% PC	2414.3 ± 106.7	0.15 ± 0.03
5% HEC 5% PC	2695.0 ± 123.5	0.13 ± 0.01

these properties will control drug diffusion and affect retention. Additionally, the formulations should exhibit pseudoplastic flow, the viscosity being sufficiently low to ensure ease of application, whereas the force required to detach the formulation from the mucosal substrate should be large, to ensure retention. This investigation therefore presents an approach for the formulation of mucoadhesive, rheologically structured gel systems based upon binary interactive polymer blends which have been shown in this study to offer both bioadhesion and improved rheological structure.

The polymers used in this study were chosen because of their pharmaceutical acceptability and their potential to form clinically advantageous interactive binary blends. Typically, the relationship between moduli (G' and G'') and oscillatory frequency for all gels may be described using the Maxwell model.[28] Interestingly, although G' and G'' increased as a function of oscillatory frequency, the extent of this was relatively small and was indicative of the plateau region.[28,29] No evidence of the terminal zone was observed. Increasing the concentration of HEC and PC either in the primary or binary gels significantly increased G', G'', and η' and may be ascribed to increased polymer entanglement and interchain association.[15] All binary gel systems exhibited loss tangent values that were lower than one which indicated that the storage modulus exceeded the loss modulus over the entire frequency range examined. This is evidence that these binary systems existed as highly entangled polymer networks in which a three-dimensional structure has been established as a result of polymer chain interpenetration and the time dependent development of secondary bond facilitated cross-links.[15] Fluid and/or fluid/gel transition states were not observed for any of the binary systems. However, single component systems containing HEC 3% w/w and PC 1% w/w exhibited fluid-gel transition behavior, whereas the higher concentrations within the single component systems were all in the gel state. The gel behavior observed for all the binary blends highlighted the enhanced rheological properties of the binary polymeric systems facilitated through HEC/PC interaction.

The storage modulus of all binary gels displayed only slight frequency dependence ($n \leq 0.26$), a characteristic of systems in which a high degree of connectivity exists between polymer

Table 5. Mechanical and Mucoadhesive Properties (Mean ± Standard Deviation) of Formulations Composed of Hydroxyethylcellulose (HEC) and Their Binary Mixtures Determined Using Texture Profile Analysis

formulation	hardness (N)	compressibility (N mm)	mucoadhesiveness (N)
3% HEC	0.56 ± 0.04	4.91 ± 0.41	0.07 ± 0.00
5% HEC	1.74 ± 0.08	15.93 ± 0.39	0.11 ± 0.00
3% HEC 1% PC	0.97 ± 0.05	9.27 ± 0.18	0.11 ± 0.01
3% HEC 3% PC	1.67 ± 0.03	16.57 ± 0.53	0.13 ± 0.01
3% HEC 5% PC	2.03 ± 0.11	19.71 ± 1.24	0.15 ± 0.01
5% HEC 1% PC	2.47 ± 0.08	23.59 ± 1.05	0.23 ± 0.00
5% HEC 3% PC	3.35 ± 0.05	32.67 ± 1.10	0.31 ± 0.03
5% HEC 5% PC	3.58 ± 0.25	36.84 ± 2.86	0.39 ± 0.02
3% HEC 1% PC + PBS	0.37 ± 0.02	2.94 ± 0.28	0.08 ± 0.00
3% HEC 3% PC + PBS	0.73 ± 0.04	9.55 ± 0.27	0.11 ± 0.00
3% HEC 5% PC + PBS	1.46 ± 0.05	12.67 ± 1.21	0.14 ± 0.01
5% HEC 1% PC + PBS	1.69 ± 0.02	17.75 ± 0.47	0.17 ± 0.00
5% HEC 3% PC + PBS	2.16 ± 0.11	23.18 ± 3.89	0.24 ± 0.00
5% HEC 5% PC + PBS	2.25 ± 0.11	28.87 ± 1.08	0.31 ± 0.01

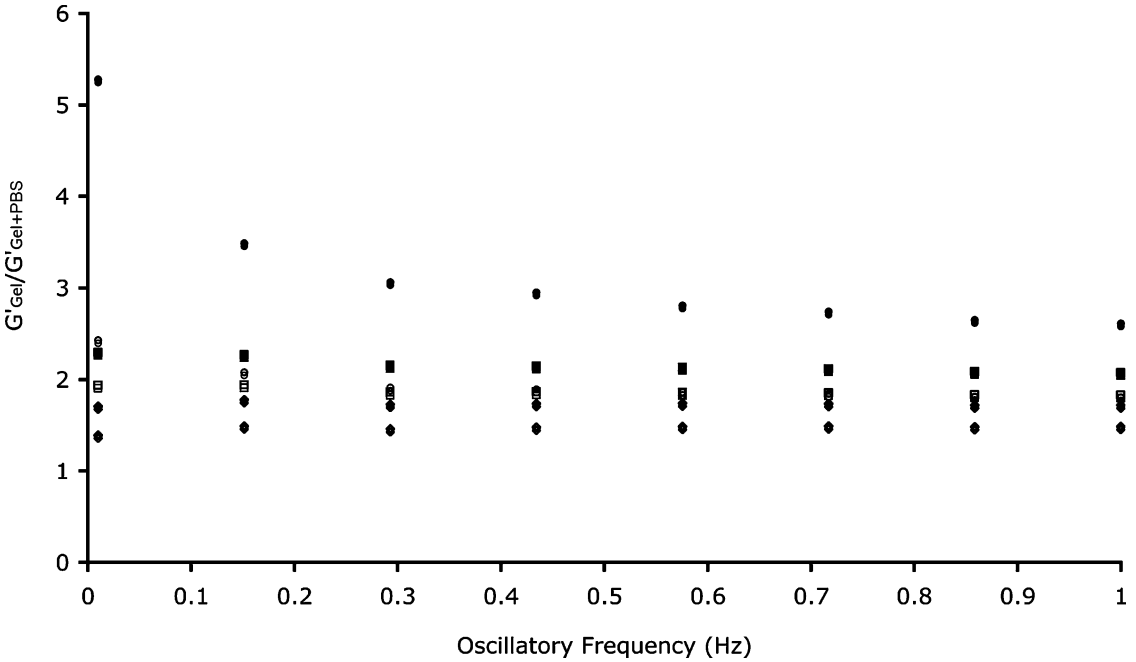

Figure 4. Frequency dependence of the ratio of the Storage Modulus of the aqueous binary interactive systems composed of HEC (3% w/w closed symbols or 5% w/w open symbols) and PC (1% w/w circles, 3% w/w squares and 5% w/w diamonds), both before and after dilution with PBS ($G'_{(gels)}$:$G'_{(gels+PBS)}$). Standard deviations have been omitted for clarity, however, and in all cases, the coefficient of variance was less than 5%.

chains.[30] Conversely, the slopes of the monopolymeric systems composed of HEC were greater, and although the magnitude of the slope decreased as a function of polymer concentration, the values were significantly greater than those of the binary systems. Consequently, the physical network developed within mono-component HEC gels was a function of oscillatory frequency and is due exclusively to physical entanglements of adjacent polymer chains.[31] HEC is a linear polymer and, in the gel state, possesses polymer chain cross-links that are a function of polymer chain overlap and secondary interactions such as hydrogen bonding.[31] The slopes of mono-polymeric gels composed of PC were low (indicative of negligible frequency dependence) and were consistent with the chemically cross-linked nature of these systems. Uniquely, the slope of the storage moduli of the binary blends was significantly decreased as a function of increasing PC concentration but unaffected by changes in HEC concentration (Table 2). The presence of highly entangled overlapping polymer chains, secondary interactions, and permanent primary bonds within the binary gel networks yielded rheological structures that were highly elastic, higher than any of the individual polymer components used in their manufacture and, in addition, partially deformable networks. The formation of binary networks importantly decreased the frequency dependence and dramatically enhanced the resultant modulus; both advantageous properties for topical mucosal drug delivery systems.[15]

The magnitude of the moduli of the binary mixtures exceeded the theoretical values (calculated by addition) and is evidence of rheological synergy between the parent polymers. Increasingly the concentrations of each polymer increased the modulus of the resultant binary systems; however, it is of interest to note that the relative increase in synergy exhibited by the various formulation platforms differed. In particular the effect of increasing the concentration of PC on the rheological synergy (and storage modulus) was dependent on the concentration of HEC, as highlighted by the significant interaction term in the ANOVA. In gels containing 3% w/w HEC, increasing PC concentration enhanced the modulus of the binary gels in a pseudolinear fashion. However, in gels containing 5% w/w HEC, the increase in modulus following the increase in PC concentra-

tion from 1 to 3% w/w was significantly greater than for comparator gels containing 3% HEC. This infers that greater polymer−polymer interaction occurred whenever the % ratio of HEC to PC was greater. The increase in modulus upon further raising the concentration of PC from 3 to 5% w/w was comparatively lower and, although the actual modulus values were larger, was statistically similar to that which occurred in the presence of 3% w/w HEC. The lack of linearity in binary gels containing 5% w/w HEC and the various concentrations of PC may be attributed to the insoluble nature of the networks at higher concentrations of each polymeric component; that is, in these situations, PC was physically dispersed in the gel network. In this, the gain of modulus that was achieved by dispersion of solid PC (5% w/w) into the HEC network was comparatively less than that observed whenever network formation was promoted the gel state.

The administration of topical mucosal drug delivery systems is typically performed by extrusion of the formulation from the applicator, e.g., syringe, container, or onto the target site. Topical application of gels therefore requires knowledge of the flow behavior following exposure to both compressional and torsional shearing stresses. Such formulations should also preferably undergo shear thinning to aid expulsion from the delivery system and possess suitable spreading properties to facilitate contact with the host epithelium.[15,19] Conversely, after application, gels should possess a high resistance to deformation (high viscosity) to ensure that there is suitable resistance to the dilution and shearing stress effects experienced at the site of application. In this investigation, the mechanical (compressional flow) properties and (torsional) flow rheological properties have been uniquely used to determine the compressional and shear flow properties of the gel systems.[19] These techniques allowed the maximum resistance to compressional deformation (hardness), the work required to compress the sample (compressibility), and the shear-thinning properties of the gels to be defined. In particular, the relationship between the ease of application of pharmaceutical formulations using a syringe applicator and the compressional flow properties and, additionally, the relationship between the compression and torsional flow properties have been previously reported.[19] These techniques are therefore particularly useful in evaluating the ease of application of the topical mucosal drug delivery systems. Increasing the concentration of each polymer increased the hardness, compressibility, and consistency of the primary and binary gels and may be accredited to increased polymer entanglement.[15,31] As expected (from the dynamic measurements), the gel consistency, hardness, and compressibility of the binary polymer systems were greater than the sum of the individual contributions, illustrating rheological synergy between HEC and PC. As before, the effects of the binary mixtures on rheological synergy were dependent on the ratio of HEC to PC and on the concentration of HEC. In accordance with the data derived from dynamic measurements, the restricted synergy associated with the gel composed of 5% w/w each of HEC and PC may be accredited to semisolid formation, thereby reducing the propensity for polymer−polymer interactions at the molecular level. In addition to the gel consistency, the pseudoplastic index (n), a measure of the ease of shear thinning,[24,32] was derived from the experimental flow data. As the value of the pseudoplastic index decreases, there is a greater decrease in viscosity as a function of increasing shear rate. All binary mixtures (and monopolymeric gels composed of PC) displayed low pseudoplastic index values and would therefore be suitable for application using an extrusion applicator, facilitating spreading of the host epithelium. It should be noted that, following application, PC gels would be unsuitable, the low viscosity and elasticity offering little resistance to product removal from the site of application.

An essential property that governs the clinical performance of topical mucosal gels is the ability to adhere to host epithelium and hence provide residency during the therapeutic period.[33] Mucoadhesive formulations of limited viscosity have been employed for this purpose; however, these systems frequently do not possess sufficient rheological structure to resist the forces experienced at the site of application. HEC and, in particular, PC have been previously reported to exhibit moderate and strong mucoadhesive properties, respectively.[18,34] In this study, the mucoadhesive properties of the various formulations were examined using a test (the mucin disk method) that has been previously employed by the authors for the assessment of the comparative mucoadhesive properties of candidate formulations.[1,35] The magnitude of the mucoadhesive properties (mucoadhesiveness) of the binary interactive mixtures under examination, particularly those containing 5% w/w HEC and 1−3% w/w PC, were similar to those which in previous investigations were proven to provide excellent retention within the periodontal pocket[1] and on the gingiva.[2] As a result, it may be suggested that the clinical retention of the binary mixtures would be acceptable.

It is accepted that one of the major challenges for topical mucosal drug delivery systems designed for use within the oral cavity or the vagina is the deleterious effect of host secretions fluids on product rheology and hence on product retention (and the prevention of product leakage). Accordingly, the effects of dilution, representative of that encountered in vivo[36] on the physicochemical properties of the candidate gel systems were examined. Importantly, the effects of dilution on the rheological and mucoadhesive properties of the binary interactive blends described in the investigation were less pronounced than in previous reports. For example Chang et al.[37] previously reported a 10-fold decrease in the storage moduli of thermoresponsive gels composed of poloxamer and PC, whereas in this investigation, the storage modulus decreased by between 1.4- and 5.3-fold. This difference in performance may be directly attributed to the greater interaction of HEC and PC in comparison to the system described by Chang et al., which is unsurprising given the self-aggregating properties of poloxamers. Moreover only a limited number of investigations have focused on the effect of oscillatory frequency on the dilution effects. Interestingly, the effect of dilution was shown to be dependent upon the oscillatory frequency, which suggests that the dilution may have more significant effects when the formulation is experiencing stresses over a wide range of time scales, e.g., chewing and talking. Ideally, following dilution, formulations should be independent of oscillatory frequency and hence independent of the times over which the forces are applied at the site of application. These platforms would possess more in-vivo stability and hence a more predictable response to dilution. Increasing the concentration of HEC and PC within the binary mixtures significantly reduced the frequency dependence following dilution. These effects may be ascribed to the highly elastic behavior observed by the binary interactive blends and their ability to absorb/expand fluid with a limited effect on the network structure. This ability subsequently resulted in minimal changes in the mechanical and mucoadhesive properties of the gels.

Conclusions

In this study, gels composed of binary interactive polymeric components have been formulated and the rheological and mucoadhesive properties characterized, both before and following dilution (to simulate dilution in vivo). Rheological synergy was observed in the binary gels, resulting in a wide range of mucoadhesive, mechanical, and rheological (flow and dynamic) properties. It is suggested that selected binary gels described in this study exhibited suitable rheological and mucoadhesion properties, even after dilution, further highlighting their potential clinical promise. In particular, binary interactive gels composed of HEC (5% w/w) and PC (1−3% w/w) offered particular promise as platforms for topical mucosal drug delivery system due to their excellent elasticity and low loss tangent, particularly following dilution, acceptable flow properties (in both torsional and tensile modes) thereby enabling ease of administration and clinically relevant mucoadhesive properties.

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