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Design of binary polymeric platforms containing ι-carrageenan and hydroxypropylcellulose for use in cataract surgery

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Abstract

This study describes the design and characterisation of the rheological and mechanical properties of binary polymeric systems composed of 2-Hydroxypropylcellulose and ι-carrageenan, designed as ophthalmic viscoelastic devices (OVDs). Platforms were characterised using dilute solution, flow and oscillatory rheometry and texture profile analysis. Rheological synergy between the two polymers was observed both in the dilute and gel states. All platforms exhibited pseudoplastic flow. Increasing polymer concentrations significantly decreased the loss tangent and rate index yet increased the storage and loss moduli, consistency, gel hardness, compressibility and adhesiveness, the latter being related to the *in-vivo* retention properties of the platforms. Binary polymeric platforms exhibited unique physicochemical properties, properties that could not be engineered using mono-polymeric platforms. Using characterisation methods that provide information relevant to their clinical performance, low-cost binary platforms (3% hydroxypropylcellulose and either 1% or 2% ι-carrageenan) were identified that exhibited rheological, textural and viscoelastic properties advantageous for use as OVDs.

Keywords: Ophthalmic Viscoelastic Devices; ι-carrageenan; Hydroxypropylcellulose; Viscoelastic, Adhesiveness, Interaction Parameter

1. Introduction

Cataract formation is one of the most common causes of vision loss, being commonly observed as a result of ageing, certain diseases (e.g. diabetes mellitus, Wilson's disease), and direct injury to the lens by a foreign object or by blunt trauma to the eye. In most cases the cataract interferes with the visual axis and requires removal. (Kawaguchi T., Mochizuki M., K. & N., 2007; Olson, Mamalis, Werner & Apple, 2003). Due to surgical advances, blindness caused by cataracts are considered to be highly treatable through extraction of the cataract and replacement with an intraocular lens (IOL) which, in turn, restores vision thus compensating for the loss of the lens (Andrews, Gorman & Jones, 2005b; Collins, Gaster, Krol, Colling, Kirk & Smith, 2003; Olson, Mamalis, Werner & Apple, 2003). One of the most popular methods that is associated with the replacement of the lens with IOLs is phacoemulsification, a process in which the hardened nucleus of the crystalline lens is emulsified and removed through a small excision within the eye (Andrews, Gorman & Jones, 2005a; Dick & Schwenn, 2000; Lloyd, Faragher & Denyer, 2001). This microsurgery must avoid injury to the corneal endothelium (present in the anterior segment of the eye); a single layer of cells that does not have the ability to regenerate. Since the introduction of phacoemulsification in 1967, evidence has shown that corneal epithelial damage may occur using this method for a number of reasons including contact of the IOL or medical instruments with the corneal epithelium (Binder, Sternberg, Wickham & Worthen, 1976; Cutler Peck et al., 2009; Irvine, Kratz & O'Donnell, 1978). Importantly, if injured, blindness may result (Lloyd, Faragher & Denyer, 2001).

Ophthalmic Viscosurgical Devices (OVDs) are viscoelastic materials that may be easily inserted into/removed from the eye, maintain ophthalmic intraocular space (within the anterior chamber) and additionally, offer protection to the endothelial cell layer from mechanical trauma (Hosny, Eldin & Hosny, 2002). These devices are widely used to maintain the integrity and viability of this barrier, not only on cataract surgery but also in the

treatment of retinal detachment (Andrews, Gorman & Jones, 2005a; Kiss et al., 2003). Thus, cataract surgery and other operations involving the anterior chamber of the eye have benefited from the use of OVDs

Whilst there are several commercially available OVDs (Arshinoff & Jafari, 2005b), their design (and indeed the choice of polymers for use as OVDs) has not been specifically performed within the context of the rheological demands of these systems (Andrews, Gorman & Jones, 2005a). The optimal rheological performance of OVDs may not be necessarily achieved using mono-polymeric systems and, as a result, one strategy to improve this rheological discrepancy involves the use of binary (or higher) mixtures of polymers in which rheological synergy may be achieved due to an interaction between the chosen polymers (Andrews & Jones, 2006). Such synergy may be successfully exploited to produce platforms that offer an enhanced range of rheological properties that may be applicable to the formulation of OVDs (Andrews, Gorman & Jones, 2005a; Dick, Krummenauer, Augustin, Pakula & Pfeiffer, 2001). The rheological properties of the candidate OVDs may then be finely tuned by the choice of the concentrations of the polymeric components and their ratio.

Therefore, the primary aim of this study was to design interactive blends of polymeric components that may be engineered to offer a more appropriate range of mechanical (rheological, compressional flow and adhesive) properties; properties that are of specific importance to their performance as OVDs. In particular the polymeric blends investigated, ι-Carrageenan and Hydroxypropylcellulose, have been chosen due to their known biocompatibility, pharmaceutical acceptability and also because these will be less expensive than those currently used as OVDs (e.g. hyaluronic acid, chondroitin sulfate) (Arshinoff & Jafari, 2005b; Baino, 2011).

2. Material and Methods

2.1 Materials

Iota (ι)-Carrageenan (Commercial Grade, Type II) and Hydroxypropylcellulose (HPC, molecular weight 370,000 g mol^{-1}) were purchased from Sigma-Aldrich (Poole, Dorset, UK). All other chemicals were of AnalaR grade or equivalent and were purchased from Sigma-Aldrich (Poole, Dorset, UK)

2.2 Preparation of Mono and Binary Polymeric OVDs

Mono and binary polymeric systems were prepared by slowly adding the required amount of polymer (ι-Carrageenan and/or HPC) to the appropriate amount of water and mixed using a yellow line mechanical stirrer (2000 rpm). Manufactured systems were then left to equilibrate for 24 hours before testing. All systems were tested within 72 hours.

2.3 Dilute solution (viscometry) studies of mono and binary polymer systems

Viscometric measurements of polymer solutions were carried out using Rheotek Ostwald U-tube viscometers size A-D. The temperature was regulated at 37°C ± 0.5 °C by a circulating bath. Once added to the U-tube, solutions were allowed 15 minutes to equilibrate to temperature before analysis. The kinematic viscosity (υ, mm^2s^{-1}) of the solution at appropriate efflux times was calculated as follows:

$$\upsilon = kt \qquad \text{(Equation 1)}$$

where: k is the tube constant and t is the flow time of the solutions (s)

From this the relative viscosity (η_{rel}) is determined:

$$\eta_{rel} = \frac{\upsilon}{\upsilon_o} \qquad \text{(Equation 2)}$$

Where υ_0 is the kinematic viscosity of the solvent.

The reduced viscosity is calculated (equation 3), which when extrapolated to zero concentration defines the intrinsic viscosity [η]:

$$\eta_{red} = \frac{\eta_{rel}-1}{C} = \frac{\eta_{sp}}{C} \quad \text{(Equation 3)}$$

where C is the concentration of the polymer in g dL^{-1} (Harding, 1997). Five replicate measurements were performed for each solution.

Modelling of viscometry data for mono and binary polymer solutions was performed using the second power exponent of Huggin's equation, as defined below (Harding, 1997; Huggins, 1942):

$$\frac{\eta_{sp}}{C} = [\eta] + K_H[\eta]^2 C \quad \text{(Equation 4)}$$

where, in addition to the previously defined terms, K_H is the Huggins constant.

Determinations of Huggin's constants and the intrinsic viscosities for each polymer/mixture were performed using linear regression analysis setting $\frac{\eta_{sp}}{C}$ and C as the dependent and independent variables, respectively.

To ascertain polymer-polymer miscibility the interaction terms (α) for the binary mixtures of HEC and ι-carrageenan were calculated using the following equation (Sun, Wang & Feng, 1992).

$$\alpha = K_m - K_{HPC}[\eta_{HPC}]^2[W_{HPC}]^2 + K_{Carr}[\eta_{Carr}]^2[W_{Carr}]^2 + \frac{2\sqrt{K_{HPC}K_{Carr}}[\eta_{HPC}][\eta_{Carr}]W_{HPC}W_{Carr}}{([\eta_{HPC}]W_{HPC} + [\eta_{Carr}]W_{Carr})^2}$$

(Equation 5)

where:

K_{HEC} and K_{Carr} are the Huggin's constant for HPC and iota-carrageenan, respectively

K_m is the Huggin's constant of the binary blend

$[\eta_{HPC}]$ and $[\eta_{Carr}]$ are the intrinsic viscosities of HPC and iota-carrageenan, respectively.

$W_{HEC}\ and\ W_{Carr}$ are the weight fractions of HPC and iota-carrageenan, respectively.

2.4 Continuous Shear (flow) rheometry

Continuous shear analysis was performed at 37°C using a TA AR2000 rheometer. The choice of plate size was determined by sample viscosity and a gap size between upper and lower plate of 1000μm was used. After application to the lower plate samples were allowed to equilibrate for 15 minutes. The shear stress was applied over a predetermined range of shear rates, which was governed by sample viscosity. The shearing rate was increased over a period of 150s, held at the upper limit for 10s and then decreased over 150s. The flow properties ascertained were the average of five replicates (Jones, Brown & Woolfson, 2001) (Bruschi ML, Jones DS, Panzeri H, Gremião MPD, Freitas O & EHG., 2007). Flow curves were fitted using the Ostwald-de-Waele equation (power law equation), represented by Equation 6 (Jones, Lawlor & Woolfson, 2002):

$$\sigma = k\gamma^n \qquad \text{Equation 6}$$

where:

σ is the shear stress (Pa),

k is the consistency index ($Pa.s^n$),

γ is the shear rate (s^{-1})

n is the flow exponent

2.5 Dynamic (oscillatory) rheological analysis

Oscillatory analysis was performed at 37°C using a TA AR2000 rheometer. The geometry used for analysis was chosen dependent on sample viscosity with a gap size of 1000μm

employed. Samples were applied to the lower plate and allowed to equilibrate for 15 minutes. For each sample the Linear Viscoelastic Region (LVR) was determined via a stress sweep at the upper and lower frequency. Frequency sweeps were performed from 0.1 to 10Hz within the LVR region. The TA Instruments software, Rheology Advantage, was used to calculate the storage modulus (G'), loss modulus (G''), dynamic viscosity (η'), and loss tangent (tan δ) (Jones, Laverty & Andrews, 2015; Jones, Muldoon, Woolfson & Sanderson, 2009). At least 5 replicate measurements were made in all occasions.

The frequency dependence of the elastic modulus was modelled through a power law relationship as previously reported (Ramkumar, Battacharya, Menjovar & Huang, 1996):

$G_f = Kf^n$ Equation 7

G (Pa) is the storage modulus

f (Hz) is the oscillatory frequency

n is the power law index

K (Pa) is the gel strength (at a frequency of 1Hz)

Calculation of rheological synergy within binary polymer blends using oscillatory data at a defined frequency (10Hz) was performed according to the method reported by (Andrews, Gorman & Jones, 2005a; Gallo & Hassan, 1990). In this, the difference between the observed and theoretical storage moduli for the binary systems is calculated as follows:

$\Delta G' = \Delta G'_{mixture} - (\Delta G'_{CAR} + \Delta G'_{HEC})$ Equation 8

2.6 Evaluation of mechanical properties using texture profile analysis

The mechanical properties of the candidate OVDs were determined by texture profile analysis (TPA) using a TA-XT2 Texture Analyser (Stable Micro Systems, Surrey, England) in compression mode as previously described (Bruschi ML, Jones DS, Panzeri H, Gremião MPD, Freitas O & EHG., 2007; Jones, Lawlor & Woolfson, 2002). In this McCartney bottles were filled with approximately 16 g of each formulation and centrifuged to remove entrapped air. A polycarbonate probe (10 mm diameter) was then inserted, removed and then reinserted into the samples at a rate of 10 mm s^{-1} to a depth 15 mm. At least five replicates of each sample were analysed at 37 ± 0.1ºC. From the resultant force-distance plot the hardness, compressibility and adhesiveness of the polymeric platforms were calculated (Jones, Lawlor & Woolfson, 2002; Jones, Woolfson & Djokic, 1996):

2.7 Statistical Analysis

Polymer concentration and type effects on consistency and flow indexes (derived for the Ostwald-de-Waele model), the viscoelastic properties (G', G", tan δ and η') at five representative frequencies (0.595; 3.565; 6.04; 8.515 and 10.0 Hz), gel strength and the textural (mechanical) properties (hardness, compressibility and adhesiveness) were statistically compared using a two-way ANOVA. Individual differences between the means were identified using Tukey's Honestly Significant Difference test. Linear regression analysis (in association with the Analysis of Variance and correlation analysis) was employed to confirm the validity of the linear relationship described in equation 4. In all cases, a significance level of $p<0.05$ was accepted to denote significance and therefore individual probability values are not cited. Measurements were performed on at least five replicate samples.

3. Results and Discussion

The use of OVDs has increased in recent years due, in part, to their ability to both offer increased protection to the corneal endothelium and to maintain the anterior space of the eye (Andrews, Gorman & Jones, 2005b; Arshinoff & Jafari, 2005b; Ho & Afshari, 2015). It has been reported that ideally OVDs should exhibit a range of properties, including ease of administration and removal, to offer protection of the corneal endothelium and intraocular tissues and possess the ability to occupy and maintain the intraocular space (Andrews, Gorman & Jones, 2005b; Dick & Schwenn, 2000). Two qualitative terms that are often used to categorise OVD products are *cohesive* and *dispersive*. Cohesive OVDs are high viscosity products that act to stabilise the ocular environment and maintain the ocular space. Ideally, cohesive systems should be shear thinning and should rheologically recover after the application of stress (during administration) to present a viscous structure that resists deformation. Conversely, dispersive OVDs are low viscosity systems that readily flow over and adhere to the ocular tissues and act to offer protection to the tissues during phacoemulsification (Andrews, Gorman & Jones, 2005b; Mamalis, 2002). From this description it may be discerned that optimisation of the rheological properties of OVDs is essential to ensure clinical performance. In addition, given that many commercial products do not exhibit the required rheological properties, an opportunity exists to develop low-cost replacement products that offer these properties. Currently available OVDs are expensive and are primarily composed of a single polymeric component, thus limiting the opportunities to engineer the prescribed rheological properties. In this study OVDs have been designed that are inexpensive and offer a wider range of rheological properties that are more appropriate to the clinical demands of such systems. The two polymers examined in this study are pharmaceutically acceptable and they (or chemically-related derivatives) have been used as platforms for ocular application. For example, cellulose ethers (of which hydroxypropylcellulose is a member) have been used as vitreous substitutes (Baino, 2011),

as ocular bandage contact lenses (Patchan et al., 2016) and as platforms for drug delivery to the front of the eye (Makwana, Patel & Parmar, 2016; Sultana, Aqil, Ali & Zafar, 2006). Verification of the tolerance of injections of a cellulose ether (hydroxypropylmethylcellulose) has been described by Robert *et al.* (Robert, Gloor, Wachsmuth & Herbst, 1988). Similarly the *in vivo* ocular safety of carrageenan has been reported (Fernandez-Ferreiro et al., 2015).

Thus, the rational selection of the polymeric components and their ratios in this study has enabled the development of polymeric systems whose rheological properties are more aligned with the clinical demands. This approach therefore offers a new strategy for the development of ocular implants and will be of great interest to the academic, clinical and industrial communities.

3.1 Dilute solution rheometry of mono and binary polymer systems

Dilute solution rheometry (viscometry) was employed to identify polymer-polymer miscibility, a phenomenon that is indicative of interactions between the two polymeric components. Using this approach plots of the reduced viscosity against concentration of each of the mono and binary dilute polymer solutions were examined and shown to be linear over specific concentration ranges ($r>0.98$), enabling application of Huggin's equation to the data sets (Figure 1). It should be noted that the applicability of other models that are frequently used to define the dilute solution properties of polyelectrolytes, notably those described by Fedors and Fuoss (Jones, Laverty, Morris & Andrews, 2016; Morariu, Brunchi & Bercea, 2012) was examined through linear regression analysis and correlation analysis. However, the goodness of fit of these models was inferior to that associated with the Huggins plot. As shown in Figure 1, both the nature of the polymer and the composition of the binary mixtures significantly affected their reduced viscosities. Application of equation 5 allows evaluation of the miscibility between ι-Carrageenan and HPC to be determined (Sun, Wang & Feng, 1992). As may be observed in Figure 2, the majority of blends exhibited an

interaction parameter that was significantly greater than 0; indicative of polymer-polymer miscibility and hence interaction. The greatest interaction parameter was associated with the 80:20 HPC-i-Carrageenan blend. These results have confirmed that, with the exception of blends composed of 30:70, 20:80 and 10:90 HPC-ι-Carrageenan, an interaction between these two polymers occurred in the dilute state, the extent of which was dependent on blend ratio. Dilute solution viscometry has been previously used to examine the interactions between two polymers. For example, Bumbu *et al.* (2005) employed dilute solution viscometry to investigate the interaction between HPC and copolymers of maleic acid. Their findings suggested that at certain ratios an interpolymer complex was formed between both polymers (Bumbu, Vasile, Chitanu & Staikos, 2005). Dilute solution rheometry has consequently provided evidence that binary blends of HPC and ι-Carrageenan are interactive and may therefore offer unique rheological properties that may be beneficial to this proposed application.

3.2 Flow rheometry and textural analysis of mono and binary polymer systems

The flow and textural properties of both the mono and binary polymeric formulations are presented in table 1. Modelling of the flow properties using the Cross model (Cross, 1965) was performed however the precision of this model concerning the prediction of the zero-shear rate viscosity was low (the coefficient of variation frequently exceeding 0.2). Accordingly, the relationship between shear stress and shear rate was modelled using the Ostwald de Waele equation, allowing the flow properties to be described in terms of the consistency and the flow index. The flow index of all candidate OVDs approached 0 and are therefore pseudoplastic (shear thinning) in nature, a beneficial property for the chosen application. Increasing the concentrations of ι-Carrageenan and HPC significantly increased the consistency of the OVDs. Furthermore, a statistical interaction between these two parameters was observed and was due to a disparity in the relationship between the effects of each polymer on the consistency. Hence, increasing the concentration of ι-carrageenan

from 0.5 to 1 to 2% w/w increased the consistency of OVDs containing 2-4% HPC. In the presence of 5% HPC, addition of 0.5 and 1% iota-carrageenan significantly increased the consistency, conversely, in the presence of 2% polymer the consistency decreased.

In a similar fashion to flow rheometry, increasing HPC and/or ι-carrageenan concentrations significantly increased the hardness, compressibility and adhesiveness of the candidate ocular implants. A statistical interaction was again noted between the two primary factors (concentrations of both HPC and ι-carrageenan), which was due to the disparity in the effects of increasing ι-carrageenan concentration on the textural parameters of platforms of each concentration of HPC. Contrary to other polymer combinations, increasing ι-carrageenan concentration from 1-2% w/w (but not from 0.5-1% w/w) in systems containing 5% w/w HPC significantly lowered the hardness, compressibility and adhesiveness of the various OVDs. The flow and textural (hardness and compressibility) properties of OVDs are primary determinants of their clinical performance, defining the ease of application to and the ability to fill the ocular space and the ease of removal of the OVD from the ocular space at the termination of the clinical procedure. In particular, the compressibility provides a direct measurement of the resistance of the formulation to a linear stress and is directly related to the clinical scenario in which the administration of the OVD to the anterior space is performed using a syringe. The combination of HPC and ι-carrageenan allowed OVDs to be formulated to offer wide ranges of flow and textural properties that were not observed by the mono-polymeric counterparts. Moreover, this study has shown that the desired rheological and textural properties may be engineered through the manipulation of both the total polymer concentration and the ratio of the polymeric components. The textural parameters complement the results derived from flow rheometry. With respect to the clinical application, platforms showing lower consistencies, hardness and compressibility will facilitate administration (typically using a syringe) and flow within the ocular chamber and enable removal post-surgery. The pseudoplastic properties

of the platforms will enable structural recovery following implantation and will ensure stabilisation of the ocular space. The observed rheological and textural synergies are accredited due to interactions between the two polymer components. Finally, of particular interest is the adhesiveness of the platforms under investigation. Importantly, OVD platforms should adhere to and subsequently protect the corneal endothelium (Neumayer, Prinz & Findl, 2008). This study has uniquely described the adhesive properties of the polymeric systems under investigation using texture profile analysis. Whilst not a direct measurement of mucoadhesion, a number of studies have shown the strong correlation between mucoadhesion and adhesiveness and therefore the information from this study is of relevance to their clinical performance (Irwin, McCullough & Jones, 2003; Jones, McMeel, Adair & Gorman, 2003; Jones, Woolfson, Brown, Coulter, McClelland & Irwin, 2000). The range of adhesiveness values displayed by the polymeric platforms under investigation is considerable; modification of the ratio of HPC: ι-carrageenan facilitating the design of platforms with defined adhesiveness properties. Ideally, OVDs should display adhesive properties that facilitate interaction with the corneal endothelium but do not damage the endothelium during the process of removal of the OVD. In this respect the platforms based on 4%w/w HEC and 2% ι-carrageenan and 5% HEC and 1% or 2% ι-carrageenan would be deemed unsuitable.

3.3 Viscoelastic properties of mono and binary polymer systems

The effects of polymer type, concentration and oscillatory frequency on the storage modulus, loss modulus and loss tangent of the various mono and binary polymeric platforms are shown in Figure 3 and Tables 2, 3 and 4. Furthermore, information on the viscoelastic properties were derived through calculation of the gel strength and power law index, both derived from the relationship between storage modulus and oscillatory frequency. Increasing oscillatory frequency and polymer concentration significantly increased the storage modulus and the loss modulus until a plateau was observed and

reduced the loss tangent of the various platforms. The effects of increasing polymer concentration on the observed gel strength, moduli and loss tangents may be accredited to enhanced strength and frequency of polymer-polymer interactions (Halacheva, Adlam, Hendow, Freemont, Hoyland & Saunders, 2014; Larsen, Bjornstad, Pettersen, Tonnesen & Melvik, 2015). In so doing the resistance to deformation increased. Mono-polymeric HPC (1-5% w/w) and mono-polymeric ι-carrageenan (0.5-2.0% w/w) exhibited viscoelastic properties that were concentration dependent, exhibited loss tangents that were less than 1 yet their magnitudes of the storage moduli were modest. By contrast the binary compositions exhibited significantly greater storage and loss moduli and displayed low loss tangents that were representative of highly elastic gel systems (Winter & Chambon, 1986). The binary combination of polymers produced polymeric platforms in which there was rheological synergy; the observed storage modulus (and loss modulus) of the binary systems statistically exceeding the rheological properties that would be observed by simple addition of the individual components (Table 5). A statistical interaction was observed between the two polymers with respect to the interaction parameter. In this the magnitude of rheological synergy was dependent on polymer type and concentration. Increasing concentration of ι-carrageenan significantly increased the observed rheological synergy in platforms containing $\leq$ 4% but not 5% w/w HPC. Furthermore, the extent of the increased synergy was greatest by increasing the concentration of ι-carrageenan from 1-2% w/w in platforms containing 1 and 2% w/w HPC. Similarly increasing the concentration of ι-carrageenan in platforms containing 3 and 4% HPC led to an increased but lesser synergy whereas in platforms containing 5% w/w HPC, maximum synergy was observed in the presence of 1% w/w ι-carrageenan. These results may be accredited to the effects of viscosity on polymer chain mobility (Wang, Li & Pielak, 2010; Xiao, Gupta, Baltas, Liu, Chae & Kumar, 2012), the platforms of highest viscosity inhibiting polymer-polymer interactions. The power law index was examined as this provides an overview of the frequency dependence of the storage modulus of the polymeric platforms. Increasing the

concentration of ι-carrageenan within the binary platforms reduced the power law index of the candidate OVDs however the effect of HPC on this parameter was parabolic, i.e. statistically concentration independent. As a result, platforms containing 3% w/w HPC and ι-carrageenan exhibited the lowest power law index. Several platforms exhibited power law indices that were ≤ 0.01; their storage moduli being predominantly frequency independent. This property is clinically advantageous as it ensures that the rheological properties of the OVDs are maintained when exposed to oscillatory, non-destructive stresses during phacoemulsification (Dick & Schwenn, 2000; Dick, Krummenauer, Augustin, Pakula & Pfeiffer, 2001).

In the dilute solution study (Figure 2), the maximum interaction parameter was associated with the 80:20 HPC: ι-carrageenan ratio, however ratios composed of 90:10, 70:30, 60:40, 50:50 and 40:60 displayed interaction parameters that were ≥ 0. In the gel state the polymer ratios that were associated with maximum rheological synergy were dependent on the concentration of HPC but did not directly correlate with the ratios identified using dilute solution rheometry. This disparity may be explained by the inverse relationship between solution/gel viscosity and polymer chain mobility and hence the interaction between the two polymers (Fu, Pacheco & Prud'homme, 2009; Shimizu & Kenndler, 1999).

3.4 Clinical opportunities for the binary polymeric platforms as OVDs

The rheological and viscoelastic properties of the binary platforms under investigation offer significant advantages over both their monopolymeric comparators and against several commercially available systems. The need for a comprehensive understanding of the rheological, viscoelastic and related properties of OVDs has been correctly identified (Arshinoff & Jafari, 2005a; Dick & Schwenn, 2000). However, this understanding is compromised by the challenges associated with the interpretation of the methods used and

accordingly, there is a need to characterise the properties of candidate OVDs using methods that are more appropriate to understanding their clinical performance (Arshinoff & Jafari, 2005a). The types of methods that are used to assess the suitability of OVDs include conventional flow rheometry (from which the zero shear rate viscosity and flow phenotypes are derived) and the Poyer assay method, the latter being used to characterise the cohesive properties as the break point of a platform (mmHg) whenever exposed to increasing vacuum pressures (Poyer, Chan & Arshinoff, 1998). Based on these methods a classification scheme was proposed that described OVDs in terms of their viscosity (low, high, very high) and cohesive properties (low, high), with a distinct clinical requirement identified for OVDs that possess high cohesion and low viscosity (Arshinoff & Jafari, 2005a). The zero-shear rate viscosity is frequently and indiscriminately used however, in these studies, no consideration of the appropriateness of this measurement has been recorded. The mono-polymeric and binary polymeric systems described in this study were modelled using the Cross model, from which the zero-shear-rate viscosity was determined (Cross, 1965) however the precision surrounding this model was poor (coefficient of variation frequently $\geq$ 0.25). Under these conditions and indeed whenever pseudoplastic systems are under examination and the shear rate range used in the analysis results in a linear inverse relationship between log viscosity and log shear rate, extrapolation to zero-shear rate viscosity, the region in which there is a plateau in the plot of log viscosity against log shear rate, is often problematic. Therefore, it is suggested that as used in this study, the power law model should be used to determine consistency and the flow index; the former being related to viscosity and the latter a measure of pseudoplasticity. Akin to other biomedical/pharmaceutical implants, characterisation of OVDs should optimally involve the quantification of their viscoelastic properties. This allows an evaluation of the rheological response of the implants under the oscillatory stresses that may be encountered following implantation. Ideally OVDs should display high elasticity (large storage modulus, high gel strength) that is preferably frequency independent, the latter being derived from the

exponent from the power law relationship between elastic modulus and oscillatory frequency. Furthermore, an assessment of the adhesive properties of OVDs should be performed. This study specifically proposes that the above measures should be routinely used to design and optimise the performance of candidate OVDs.

The OVDs classification scheme has identified a number of limitations associated with currently available systems, which, through the use of a binary polymeric system, this study aimed to address. This rheological, mucoadhesive and viscoelastic properties of the binary systems composed of HPC and ι-carrageenan offer significant possibilities for their clinical use as OVDs. The highly elastic properties of these binary systems, tuneable by modifying the ratio of the two polymeric components, would be expected to maintain the ocular space and, in so doing, stabilise the ocular environment during lens removal and replacement (Dick & Schwenn, 2000). This is an important clinical concern. Furthermore, the thixotropic, pseudoplastic flow properties of the binary networks will facilitate both administration within the ocular space under high shear rates (akin to those that are achieved during injection) and will spread over and adhere to the corneal endothelium though mucoadhesive interactions, the latter properties being identified in this study. Surprisingly, given the potential importance to protection of the corneal endothelium, the application of mucoadhesive systems for use as OVDs has received little attention to date. It must be noted however that care should be given to the formulation of mucoadhesive OVDs as, if the mucoadhesive strength is too large, then damage to the corneal endothelium may result whenever the device is removed from the ocular space. This would therefore preclude the use of strongly mucoadhesive polymers, e.g. poly(acrylic acid), poly(methylvinylether-co-maleic anhydride) (Smart, 2005) (Andrews, Laverty & Jones, 2009) within OVDs. The systems in this study have been designed using polymers that are only moderately mucoadhesive (Andrews, Laverty & Jones, 2009). Therefore, the binary platforms formed using HPC and ι-carrageenan were engineered to offer mucoadhesive properties that were

sufficient (but not excessive) thereby facilitating protection of the corneal endothelium. Ideally, candidates should exhibit high (equilibrium) viscosity and elasticity (to maintain the integrity of the anterior chamber), low viscosity upon administration to facilitate flow over the corneal endothelium and adhesive properties to ensure interaction with the endothelium. These properties were not demonstrated by mono-polymeric systems. However, binary platforms composed of 3% HPC and either 1% or 2% ι-carrageenan displayed necessary adhesiveness, consistency, elasticity, which, in combination with the low flow index, will ensure ease of administration to and retention at the site of application and maintenance of the anterior space.

4. Conclusions

In this study, binary polymeric platforms composed of hydroxypropylcellulose (HPC) and ι-carrageenan have been prepared as candidate ophthalmic viscoelastic devices (OVDs). Characterisation of these systems was performed using methods that enabled an understanding of their physicochemical properties and, in addition, how these properties pertain to their proposed clinical application. Using viscometry, HPC and ι-carrageenan were shown to interact over a wide range of ratios. At higher concentrations, the binary systems existed as pseudoplastic gels whose compressional, viscoelastic and flow properties were engineered by modification of both the mass of polymer and the ratio of the two polymers used. Furthermore, the adhesiveness of the systems under investigation were uniquely described, a property that is relevant to their clinical interaction with the corneal endothelium. Based on the physicochemical properties, low cost, binary platforms were identified that show promise as candidate OVDs, notably those composed of 3% HPC and either 1% or 2% ι-carrageenan. Finally, this study has described the physicochemical properties, including a measurement of adhesiveness, using methods that are reproducible, repeatable and which provide information relevant to their clinical performance as OVDs. It is recommended that these methods should be employed in the development of new OVDs.

Figure legend

Figure 1. The relationship between the (mean ± standard deviation, n=5) reduced viscosity and polymer concentration. Symbols: 100:0 (Carr: HPC) circles, 90:0 (Carr: HPC) squares, 70:30 (Carr: HPC) triangles, 50:50 (Carr: HPC) crosses, 30:70 (Carr: HPC) diamonds.

Figure 2. The relationship between the (mean ± standard deviation, n=5) interaction parameter and weight fraction of ι-carrageenan in HPC: i-carrageenan binary mixtures, calculated using data from dilute solution rheometry.

Figure 3. The effect of oscillatory frequency on the (mean ± standard deviation) storage modulus of mono-polymer platforms composed of different concentrations of ι-carrageenan. Symbols: 1% w/w carrageenan (crosses), 2% w/w carrageenan (triangles), 3% w/w carrageenan (diamonds), 4% w/w carrageenan (squares) and 5% w/w carrageenan (circles). Standard deviations are included.

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Table 1. The effect of polymer concentration and ratio of hydroxypropylcellulose to iota-carrageenan on the compressional (hardness, Compressibility and adhesiveness) and flow (consistency, flow index) properties of mono and binary OVDs

Polymer components (% w/w)		**Mean (± sd) compressional properties**			**Mean (± sd) Flow properties**	
HPC	**i-Carrageenan**	**Hardness (N)**	**Compressibility (N mm)**	**Adhesiveness (N mm)**	**Consistency ($Pa.s^n$)**	**Flow Index**
1	2	0.28 ± 0.01	1.26 ± 0.03	0.83 ± 0.02	Not measured	Not measured
2	0.5	0.21 ± 0.00	0.98 ± 0.02	0.80 ± 0.01	55.91 ± 3.42	0.34 ± 0.00
2	1	0.37 ± 0.00	1.74 ± 0.02	1.21 ± 0.03	174.37 ± 4.30	0.23 ± 0.01
2	2	0.57 ± 0.00	2.81 ± 0.06	2.13 ± 0.09	216.67 ± 18.97	0.14 ± 0.00
3	0.5	0.33 ± 0.00	1.36 ± 0.01	1.21 ± 0.02	245.00 ± 4.77	0.24 ± 0.00
3	1	0.60 ± 0.00	2.79 ± 0.03	1.78 ± 0.06	382.50 ± 3.17	0.19 ± 0.00
3	2	0.91 ± 0.01	3.99 ± 0.09	2.44 ± 0.03	425.73 ± 17.33	0.17 ±0.01
4	0.5	0.40 ± 0.01	1.76 ± 0.08	1.34 ± 0.03	320.67 ± 22.55	0.25 ± 0.00
4	1	0.75 ± 0.02	3.43 ± 0.02	3.51 ± 0.09	429.10 ± 4.68	0.21 ± 0.00
4	2	1.19 ± 0.02	5.50 ± 0.30	7.16 ± 0.11	476.37 ± 6.01	0.18 ± 0.01
5	0.5	0.78 ± 0.00	3.54 ± 0.01	3.89 ± 0.06	613.80 ± 6.31	0.20 ± 0.00
5	1	1.43 ± 0.05	6.52 ± 0.09	5.52 ± 0.21	652.86 ± 12.15	0.15 ± 0.00
5	2	1.24 ± 0.01	4.75 ± 0.04	4.68 ± 0.05	534.70 ± 14.61	0.23 ± 0.00

Table 2. The effect of polymer concentration and ratio of hydroxypropylcellulose to iota-carrageenan on the storage modulus of mono and binary polymeric solutions

Polymer concentration (%w/w)		Mean (± s.d.) Storage Modulus (Pa) at defined frequencies (Hz)			
HPC	Carrageenan	0.59Hz	3.0Hz	8.0Hz	10Hz
1	0	2.91 ± 0.58	8.04 ± 0.54	14.93 ± 0.87	16.80 ± 0.84
1	0.5	20.80 ± 0.96	43.88 ± 3.65	62.88 ± 3.86	68.29 ± 4.01
1	1	70.58 ± 5.02	104.55 ± 7.21	129.07 ± 6.26	138.52 ± 6.96
1	2	315.77 ± 13.89	362.15 ± 18.92	379.20 ± 21.02	384.05 ± 16.00
2	0	47.09 ± 2.00	109.74 ± 8.22	157.78 ± 5.97	166.30 ± 7.05
2	0.5	57.00 ± 2.30	119.43 ± 7.02	165.18 ± 5.04	176.12 ± 10.06
2	1	189.06 ± 16.01	286.20 ± 10.02	348.88 ± 12.65	366.97 ± 9.54
2	2	735.40 ± 43.00	903.55 ± 44.53	999.64 ± 58.83	1020.02 ± 56.85
3	0	158.02 ± 8.89	312.46 ± 16.00	415.59 ± 15.32	439.95 ± 19.47
3	0.5	312.56 ± 10.55	537.48 ± 14.76	646.6 ± 18.62	720.69 ± 22.69
3	1	485.53 ± 16.97	697.64 ± 28.01	836.87 ± 25.32	870.53 ± 31.01
3	2	813.77 ± 21.05	978.96 ± 25.96	1039.13 ± 28.22	1053.44 ± 32.55
4	0	281.35 ± 9.37	466.79 ±12.38	535.04 ± 16.88	558.00 ± 27.82
4	0.5	407.42 ± 10.03	686.57 ± 25.63	863.31 ± 28.94	908.08 ± 31.00
4	1	638.11 ± 18.52	951.06 ± 21.08	1138.74 ± 38.55	1181.89 ± 34.02
4	2	1068.40 ± 29.00	1292.88 ± 35.04	1416.98 ± 40.02	1444.10 ± 43.05

5	0	538.97 ± 17.27	810.14 ± 19.04	906.43 ± 28.53	911.79 ± 30.12
5	0.5	860.99 ± 23.05	1349.48 ± 32.97	1648.61 ± 38.55	1704.06 ± 35.68
5	1	1156.50 ± 33.30	1633.19 ± 38.41	1857.64 ± 42.06	1918.16 ± 48.93
5	2	1374.23 ± 40.65	1656 .45 ± 43.37	1809.90 ± 48.93	1830.01 ± 36.42

Table 3. The effect of polymer concentration and ratio of hydroxypropylcellulose to iota-carrageenan on the loss modulus of mono and binary polymeric solutions

Polymer concentration (%w/w)		Mean (± s.d.) Loss Modulus (Pa) at defined frequencies (Hz)			
HPC	Carrageenan	0.1Hz	3.0Hz	6.0Hz	10Hz
1	0	1.08 ± 0.18	8.83 ± 0.22	11.42 ± 0.05	13.32 ± 0.13
1	0.5	8.82 ± 0.41	28.53 ± 0.69	33.12 ± 0.81	37.09 ± 0.24
1	1	30.50 ± 2.28	35.60 ± 2.37	39.12 ± 2.55	42.08 ± 2.89
1	2	65.22 ± 2.18	62.94 ± 2.22	61.79 ± 2.24	61.62 ± 2.30
2	0	57.34 ± 0.42	72.72 ± 0.44	80.51 ± 0.61	85.30 ± 0.46
2	0.5	53.76 ± 6.12	67.67 ± 6.99	75.57 ± 7.40	81.21 ± 7.79
2	1	88.21 ± 3.37	98.95 ± 3.51	105.17 ± 3.23	109.17 ± 3.24
2	2	162.67 ± 12.21	166.10 ± 11.93	166.30 ± 10.86	166.37 ± 9.85
3	0	135.77 ± 0.61	156.30 ± 0.52	164.37 ± 0.67	166.87 ± 1.27
3	0.5	201.67 ± 4.65	223.27 ± 5.17	231.00 ± 5.62	233.63 ± 5.92
3	1	216.00 ± 5.25	225.93 ± 3.36	228.63 ± 2.08	227.93 ± 1.33
3	2	207.73 ± 14.30	195.17 ± 12.35	187.60 ± 9.90	183.93 ± 8.61
4	0	173.63 ± 5.21	179.57 ± 4.98	176.83 ± 4.83	173.10 ± 4.69
4	0.5	249.83 ± 8.56	272.23 ± 9.31	278.97 ± 9.47	279.73 ± 8.39
4	1	286.07 ± 3.15	297.67 ± 3.12	299.43 ± 3.57	295.83 ± 3.54
4	2	221.23 ± 4.87	221.07 ± 4.17	219.80 ± 4.50	217.27 ± 2.32

5	0	268.57 ± 15.89	264.70 ± 15.58	259.30 ± 14.68	272.03 ± 11.61
5	0.5	439.90 ± 4.40	451.77 ± 4.83	447.47 ± 3.50	438.67 ± 3.20
5	1	430.97 ± 6.28	427.10 ± 10.05	415.33 ± 12.67	404.20 ± 13.73
5	2	277.40 ± 6.16	271.23 ± 5.55	270.07 ± 8.04	266.70 ± 8.33

Table 4. The effect of polymer concentration and ratio of hydroxypropylcellulose to iota-carrageenan on the loss tangent of mono and binary polymeric solutions

Polymer concentration (%w/w)		Mean (± s.d.) Storage Modulus (Pa) at defined frequencies (Hz)			
HPC	Carrageenan	0.1Hz	3.0Hz	6.0Hz	10Hz
1	0	1.51 ± 0.10	1.06 ± 0.05	0.91 ± 0.04	0.81 ± 0.03
1	0.5	0.80 ± 0.00	0.65 ±0.00	0.58 ± 0.00	0.55 ± 0.03
1	1	0.37 ± 0.00	0.34 ± 0.00	0.32 ± 0.00	0.31 ± 0.00
1	2	0.19 ± 0.00	0.17 ± 0.00	0.17 ± 0.00	0.16 ± 0.00
2	0	0.83± 0.00	0.64 ± 0.00	0.54 ± 0.00	0.49 ± 0.00
2	0.5	0.68 ± 0.00	0.56 ± 0.00	0.50 ± 0.00	0.46 ± 0.00
2	1	0.39 ± 0.00	0.34 ± 0.00	0.32 ± 0.00	0.30 ± 0.00
2	2	0.20 ± 0.00	0.18 ± 0.00	0.17 ± 0.00	0.16± 0.00
3	0	0.65 ± 0.00	0.50 ± 0.00	0.42 ± 0.00	0.38 ± 0.00
3	0.5	0.52 ± 0.00	0.42 ± 0.00	0.36 ± 0.00	0.32 ± 0.00
3	1	0.38 ± 0.00	0.32 ± 0.00	0.28 ± 0.00	0.26 ± 0.00
3	2	0.23 ± 0.01	0.20 ± 0.01	0.18 ± 0.00	0.17 ± 0.00
4	0	0.50 ± 0.00	0.39 ± 0.00	0.34 ± 0.00	0.33 ± 0.00
4	0.5	0.50 ± 0.00	0.40 ± 0.00	0.34 ± 0.00	0.31 ± 0.00
4	1	0.38 ± 0.00	0.31 ± 0.00	0.28 ± 0.00	0.25 ± 0.00
4	2	0.19 ± 0.00	0.17 ± 0.00	0.16 ± 0.00	0.15 ± 0.00

5	0	0.42 ± 0.01	0.33 ± 0.01	0.30 ± 0.01	0.31 ± 0.03
5	0.5	0.42 ± 0.01	0.33 ± 0.00	0.29 ± 0.00	0.26 ± 0.00
5	1	0.32 ± 0.01	0.26 ± 0.00	0.23 ± 0.00	0.21 ± 0.00
5	2	0.19 ± 0.01	0.16 ± 0.00	0.15 ± 0.00	0.15 ± 0.00

Table 5. The storage modulus interaction parameter, gel strength and power law index of mixtures of HPC and iota-carrageenan

Polymer Concentration (%w/w)		Mean (± sd) Rheological Properties		
HPC	ι-Carrageenan	Interaction Parameter (Pa)	Gel Strength (kPa)	Power Law Index
1	0.5	38.1 ± 3.1	0.00 ± 0.00	0.39 ± 0.01
1	1	85.5 ± 3.9	0.01 ± 0.00	0.32 ± 0.01
1	2	394.7 ± 21.1	0.03 ± 0.00	0.23 ± 0.01
2	0.5	81.1 ± 4.2	0.08 ± 0.00	0.34 ± 0.01
2	1	160.7 ± 10.8	0.22 ± 0.01	0.24 ± 0.00
2	2	665.5 ± 22.6	0.80 ± 0.03	0.10 ± 0.00
3	0.5	283.9 ± 10.4	0.40 ± 0.01	0.25 ± 0.02
3	1	399.5 ± 15.2	0.59 ± 0.03	0.17 ± 0.00
3	2	467.7 ± 12.6	0.91 ± 0.03	0.06 ± 0.00
4	0.5	386.8 ± 12.5	0.52 ± 0.01	0.24 ± 0.01
4	1	635.8 ± 26.9	0.77 ± 0.01	0.18 ± 0.01
4	2	743.4 ± 20.0	1.16 ± 0.04	0.09 ± 0.00
5	0.5	805.2 ± 19.4	1.07 ± 0.06	0.20 ± 0.01
5	1	986.6 ± 42.2	1.49 ± 0.04	0.15 ± 0.02
5	2	738.4 ± 19.2	1.40 ± 0.04	0.09 ± 0.00

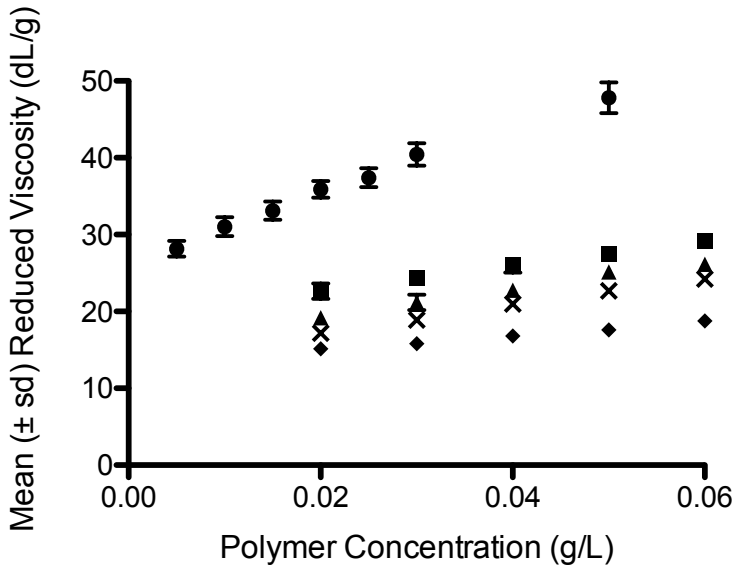

Figure 1

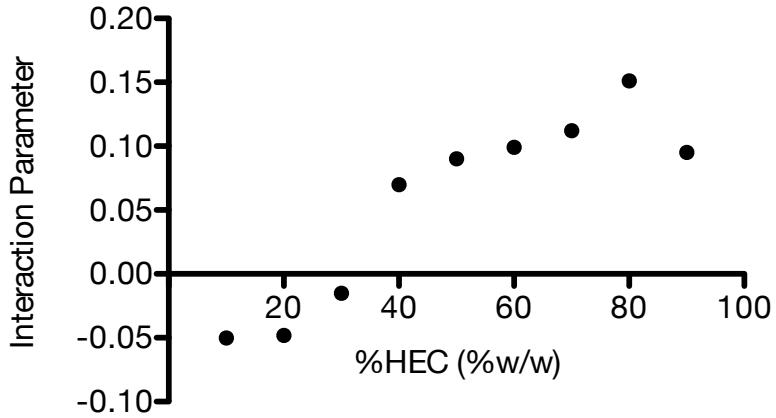

Figure 2

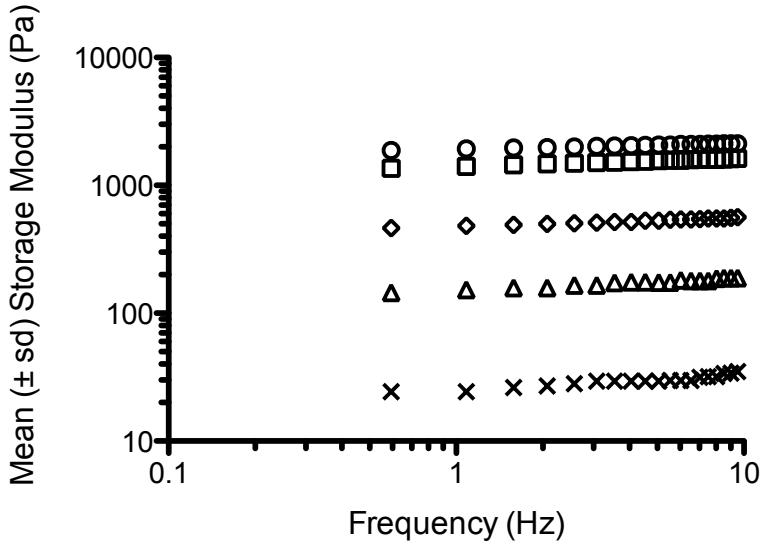
Mean (± sd) Storage Modulus (Pa)
10000
1000
100
10
0.1
1
10
Frequency (Hz)

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Figure 3