Viscoelastic Properties of Bioadhesive, Chlorhexidine-Containing Semi-Solids for Topical Application to the Oropharynx

David S. Jones,[1,2] A. David Woolfson,[1] and Andrew F. Brown[1]

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Purpose. This study examined the viscoelastic properties of bioadhesive, chlorhexidine-containing semi-solid formulations, designed for topical application to the oropharynx.

Methods. Oscillatory rheometry was performed using a Carri-Med CSL^2-100 rheometer at 20.0 ± 0.1°C in conjunction with parallel plate geometry (2 cm diameter, 0.5 mm sample thickness). Samples were subjected to a constant strain (6.5×10^{-3} rad) and defined viscoelastic parameters, namely storage modulus (G′), loss modulus (G″), loss tangent (tan δ) and dynamic viscosity (η′), measured over a defined frequency range (0.01–1.0 Hz).

Results. As the oscillatory frequency was increased, G′ G″ of all formulations increased, whereas both η′ and tan δ significantly decreased. The magnitude of increase of G′ and G″ as a function of frequency was relatively small, indicating that, in general, the formulations were non-cross-linked elastic systems. Increasing concentrations of HEC, PVP and PC significantly increased G′, G″, η′ yet decreased tan δ, observations that may be attributed to the physical state of each polymer in the formulations. Formulation elasticity increased (i.e. tan δ decreased) as a result of increased entanglement of polymeric chains of dissolved components (i.e. HEC and PVP) and the restrained extension of swollen, cross-linked chains of PC. Additionally, in formulations where the saturation solubility of PVP was exceeded and/or insufficient "free-water" was available for maximal swelling of PC, formulation elasticity increased as a result of the increasing mass of dispersed solid particles of PVP and/or PC. Formulation η′ increased due to the attendent effects of polymer chain entanglement and polymer state on overall formulation viscosity.

Conclusions. Following application to the oropharynx, the formulations will behave as elastic systems. Thus, these formulations would be expected to offer advantageous clinical properties, e.g., prolonged drug release, increased bioadhesion. However, it is noteworthy that the final choice of formulation for clinical evaluation will involve a compromise between viscoelastic characteristics and acceptable textural properties, e.g. ease of product application. This study has shown the applicability of oscillatory rheometry for both the characterisation and selection of candidate, topical bioadhesive formulations for clinical evaluation.

KEY WORDS: bioadhesion; viscoelastic; oscillatory rheometry; storage modulus; loss modulus; loss tangent; dynamic viscosity; oropharynx.

[1] The Pharmaceutical Sciences Group, School of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland, United Kingdom.

[2] To whom correspondence should be addressed. (e-mail: d.jones@qub.ac.uk)

INTRODUCTION

Typically, solutions (e.g. mouthwashes and nasal drops) containing the appropriate antimicrobial agent are employed for the treatment of infection within the oropharynx (1). This approach allows direct access of the antimicrobial agent to the site of infection at higher concentrations than may be achieved following systemic administration. However, as the retention of aqueous solutions, and hence antimicrobial agents, within the oropharynx is poor, increased retention (and hence improved clinical efficacy) may be achieved by the use of bioadhesive formulations. Reported examples of these include a multilayered tablet containing cetylpyridinium chloride, which provided super-inhibitory concentrations of this antimicrobial agent in the saliva for greater than 3 h. (2), and a bioadhesive film composed of a co-polymer (methacrylic acid and its methyl ester) which provided prolonged salivary concentrations of metronidazole for 5 h. (3). However, there are problems associated with the use of bioadhesive tablets (compacts) and films. The former, due to their relative inflexibility, may result in patient discomfort whereas bioadhesive films, whilst comfortable, are expensive to manufacture due to the need for solvent removal. These problems may be overcome by the use of bioadhesive, semi-solid preparations.

Recently, we have described the textural (mechanical) properties of novel, bioadhesive semi-solid systems containing chlorhexidine which have been designed for topical application directly onto sites of infection in the oropharynx (4). These formulations exhibited wide ranges of hardness, spreading properties (compressibility), adhesiveness (a property related to bioadhesion) and cohesiveness, parameters all directly relevant to the clinical performance of topical products (5). Textural analysis was confirmed as a useful adjunctive technique for the characterisation, and hence selection, of candidate formulations for clinical application. However, this method did not provide general information on the effects of each polymeric component on the structural rheology (viscoelasticity) of the system, an important determinant of overall product performance as described by several authors. For example, Lin *et al.* (6) have described the relationship between the viscoelastic properties of hydroxypropylmethylcellulose gels and their clinical performance. Whereas, more recently, Tamburic and Craig (7) reported the relationship between formulation loss tangent and bioadhesion. Therefore, in the development of formulations for topical application, due consideration should be given to the viscoelastic properties to ensure optimisation of product performance.

Furthermore, products designed for prolonged residence within the oropharynx will be subjected to oscillatory stresses over a wide range of frequencies as a result of normal physiological processes. Consequently, the effects of such oscillating stresses on the rheological (viscoelastic) properties of each formulation require evaluation to ensure that clinical performance is not adversely affected. In a previous publication, Jones *et al.* (5) described the viscoelastic properties of gels composed of either hydroxyethylcellulose or sodium carboxymethylcellulose and their relationship with both textural and mucoadhesive properties, important determinants of clinical performance. This study concluded that the viscoelastic properties of formulations designed for use in the oropharynx should be consistent over

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the expected range of frequencies of oscillatory stresses and, hence, the mechanical properties of such formulations will not fluctuate following exposure to such oscillatory frequencies.

Therefore, this study examines the viscoelastic behaviour of these novel, bioadhesive polymeric chlorhexidine-containing semi-solid systems using the non-destructive technique of oscillatory rheometry. It is anticipated that this information would be of further benefit for the ultimate selection of candidate formulations for clinical evaluation. The data provided by this method will therefore provide a rational basis for the selection of optimum candidate formulations.

MATERIALS AND METHODS

Materials

Hydroxyethylcellulose (Natrosol 250 HHX-Pharm), polyvinylpyrrolidone (Kollidon K90) and polycarbophil (Noveon AA1) were donated by Aqualon Ltd., (Warrington, England, U.K.), BASF (Ludwigshafen, Germany) and B. F. Goodrich Company (Clevland, Ohio, U.S.A.), respectively.

Chlorhexidine (as the diacetate salt) was purchased from Sigma Chemical Company (St, Louis, PA, U.S.A.)

All other chemicals were purchased from BDH Laboratory Supplies, Poole, U.K. and were of AnalaR, or equivalent, quality.

Manufacture of Bioadhesive Formulations Containing Chlorhexidine

Initially, a primary gel was produced by dissolving hydroxyethylcellulose (HEC; 1, 3, 5% w/w) in the required weight of phosphate buffered saline (PBS, 0.03M, pH 6.8) using a high speed mixer. This pH value was selected to avoid the potential cariogenic effects associated with acidic formulations. The primary gel was transferred onto an ointment slab and into this polyvinylpyrrolidone (PVP; 3% w/w), when required, and then polycarbophil (PC; 0.5, 1% w/w) were thoroughly mixed using a spatula. Finally, chlorhexidine (CHX; 5% w/w, as the diacetate salt, particle size < 63 μm) was thoroughly dispersed into the now semi-solid system until homogeneous. Following removal of air under vacuum, all formulations were stored in McCartney bottles at 4°C until required (4).

Oscillatory Rheometry of Chlorhexidine-Containing, Bioadhesive Semi-solid Formulations

Oscillatory rheometry was performed using a Carri-med CSL^2 - 100 rheometer with a stainless steel parallel plate geometry (2 cm diameter) at 20° ± 0.1°C. Samples were removed from their storage container, applied to the lower plate of the rheometer and allowed to equilibrate for at least 1 hour prior to analysis. This equilibration period was selected to ensure sample recovery from deformation and was based on prior knowledge of the thixotropic properties of the formulations under examination (4). The linear viscoelastic region was determined by torque sweep from 0. 1–100 Pa at frequencies of 0.01 and 1.0 Hz and was identified as the region where stress was directly proportional to strain, and, the storage modulus (G′) remained constant. A constant strain of 6.5×10^{-3} rad. was chosen for frequency sweep analyses and oscillatory measurements were performed over a frequency range of 0.01–1.0 Hz. Calculation of the storage modulus (G′), loss modulus (G″), loss tangent (tan δ) and dynamic viscosity (η′) were performed using proprietary software (TA Instruments, Leatherhead, UK).

Statistical Analysis of Results

The experimental design employed in this study was factorial ($3 \times 2 \times 2$). The effects of each polymeric component on G′, G″, tan δ and η′ at representative frequencies (0.01, 0.1142, 0.5307, 0.9478 Hz) in oscillatory rheometry were statistically evaluated using a three-way Analysis of Variance (ANOVA). Post-hoc comparisons of the means of individual groups were performed using Scheffe's test. In all cases $P < 0.05$ was accepted to denote significance (4,5).

RESULTS

The effects of each polymeric component on the oscillatory properties of all formulations at representative frequencies (0.01, 0.1142, 0.5307, 0.9478 Hz) are presented in Tables 1–4. The effects of PVP and PC on the storage modulus (G′) and loss modulus (G″) of formulations containing CHX (5% w/w) and HEC 1%, 3% and 5% are presented in Tables 1 and 2, respectively. As may be observed, both the storage and loss moduli increased as a function of oscillatory frequency in all formulations. Additionally, as the concentrations of HEC, PVP and PC were increased, the storage and loss moduli of each formulation significantly increased. Maximum and minimum (± s.d.) storage moduli (G′) were associated with formulations containing 5% HEC, 3% PVP and 1% PC (at 1 Hz) and 1% HEC, 0% PVP, 0.5% PC (at 0.01 Hz) and were 8414.7 ± 444.3 and 1.5 ± 0.1 Pa, respectively. Similarly, maximum and minimum (± s.d.) storage moduli (G″) were associated with formulations containing 5% HEC, 3% PVP and 1% PC (at 1 Hz) and 1% HEC, 0% PVP, 0.5% PC (at 0.01 Hz) and were 2594.0 ± 143.1 and 3.0 ± 0.1 Pa, respectively.

The effects of oscillatory frequency on the ratio of loss modulus to storage modulus (tan δ) of formulations containing CHX (5% w/w), PVP (0 or 3%), PC (0.5 or 1%) and either 1, 3, 5% HEC are presented in Table 3. From this, it may be observed that increasing both oscillatory frequency, and also the concentrations of each polymeric component decreased tan δ of each formulation. At all frequencies, the magnitude of the storage modulus (G′) was signifcantly greater than the loss modulus (G″) (tan $\delta < 1$) with the exception of formulations containing 1% w/w HEC, 0.5% w/w PC and either 0 or 3% PVP, in which the loss modulus (G″) exceeded the storage modulus (G′) at frequencies less than 0.4 and 0.2 Hz, respectively, i.e. tan δ exceeded unity. Maximum and minimum (± s.d.) loss tangent values were observed in formulations containing 1% HEC, 0% PVP, 0.5% PC (1.97 ± 0.26 at 0.01Hz) and 5% HEC, 3% PVP and 1% PC (0.28 ± 0.00 at 0.9478 Hz).

The effects of oscillatory frequency on the dynamic viscosities (η′) of formulations containing CHX (5% w/w), PVP (0 or 3%), PC (0.5 or 1%) and either 1, 3, 5% HEC are presented in Table 4. As the oscillatory frequency was increased, the dynamic viscosity (η′) of each formulation decreased. Conversely, increased concentrations of HEC, PVP and PC significantly increased formulation η′. Maximum (± s.d.) observed dynamic viscosity η′ was 22.0 ± 1.1 MPa.s (at 0.01 Hz) in

Table 1. The Effects of Oscillatory Frequency on the Storage Modulus (G′) of Bioadhesive Formulations Containing Chlorhexidine (5% w/w as the Diacetate Salt)

Formulation components			Mean (± s.d.) G′ (Pa) of formulations at representative oscillatory frequencies			
Concⁿ. of HEC	Concⁿ. of PVP	Concⁿ. of PC	0.01 Hz	0.1142 Hz	0.5307 Hz	0.9478 Hz
1	0	0.5	1.5 ± 0.1	10.4 ± 0.9	31.4 ± 2.0	43.8 ± 0.5
1	0	1	232.0 ± 13.8	502.3 ± 10.5	779.9 ± 40.6	923.7 ± 67.6
1	3	0.5	4.9 ± 0.0	28.4 ± 1.8	68.2 ± 4.1	85.3 ± 3.9
1	3	1	380.5 ± 24.2	686.8 ± 32.4	953.2 ± 45.6	1093.7 ± 53.3
3	0	0.5	203.8 ± 11.7	515.5 ± 20.5	868.9 ± 19.3	1016.0 ± 41.9
3	0	1	629.2 ± 26.8	1466.0 ± 106.6	2286.3 ± 100.0	2663.3 ± 114.9
3	3	0.5	229.6 ± 7.3	663.7 ± 16.9	1138.0 ± 21.5	1345.3 ± 24.1
3	3	1	750.0 ± 47.3	1892.7 ± 99.6	3006.0 ± 204.6	3548.7 ± 165.7
5	0	0.5	524.7 ± 30.9	1480.7 ± 106.9	2379.0 ± 172.2	2768.0 ± 128.9
5	0	1	1736.7 ± 141.7	3882.0 ± 254.2	5758.0 ± 339.4	6573.3 ± 401.5
5	3	0.5	847.1 ± 46.5	2221.0 ± 117.71	3420.7 ± 133.2	3908.7 ± 200.1
5	3	1	2270.7 ± 106.1	5125.7 ± 306.5	7443.3 ± 378.1	8414.7 ± 444.34

formulations containing 5% HEC, 3% PVP and 1% PC, whereas minimum (± s.d.) η′ (6.5 ± 0.1 Pa.s) was observed at 1 Hz in formulations containing 1% HEC and 0.5% PC.

Several significant statistical interactions were identified within the factorial experimental design, namely between HEC and PC and between HEC and PVP with respect to G′, G″, tan δ and η′. In these interactions, the increase in G′, G″, η′ and decrease in tan δ associated with increased concentrations of either PVP or PC was significantly greater in the presence of 5% HEC than was observed in formulations containing either 1 or 3% HEC. Hence, the effects of either PVP or PC on the rheological parameters of formulations containing 1, 3 or 5% HEC were non-additive, leading to non-linearity (4,19). Similar statistical interactions (between HEC and PC and between HEC and PVP) with respect to textural parameters (hardness, compressibility, adhesiveness, cohesiveness) have been previously reported (4).

DISCUSSION

The rheological properties of semi-solid/gel systems are important both in respect of their manufacture and ultimate clinical performance (7–10). Traditionally, continuous shear viscometry and, more recently, textural analysis, have been employed to characterise the rheological properties of semi-solid pharmaceutical products (4,11,12). However, these methods are destructive and information cannot be conveyed concerning the structure of the sample. Consequently, non-destructive rheological techniques, e.g. oscillatory rheometry, have been employed to characterise the structural rheology (viscoelasticity) of pharmaceutical gels and semi-solids (5,8,13). Oscillatory rheometry was therefore employed in this study to characterise the effects of polymeric formulation components on the viscoelastic properties of novel, bioadhesive semi-solid formulations for topical application to the oropharynx.

The formulations under examination displayed wide ranges of each viscoelastic parameter under investigation that were both polymer concentration dependent and also dependent on the oscillatory frequency. The relationship between G′ and oscillatory frequency is consistent with the Maxwellian description of the response of viscoelastic materials to oscillatory stresses (14). Interestingly, whilst the magnitudes of both G′

Table 2. The Effects of Oscillatory Frequency on the Loss Modulus (G″) of Bioadhesive Formulations Containing Chlorhexidine (5% w/w as the Diacetate Salt)

Formulation components			Mean (± s.d.) G″ (Pa) of formulations at representative oscillatory frequencies			
Concⁿ. of HEC	Concⁿ. of PVP	Concⁿ. of PC	0.01 Hz	0.1142 Hz	0.5307 Hz	0.9478 Hz
1	0	0.5	3.0 ± 0.1	14.4 ± 0.9	31.0 ± 1.5	38.4 ± 0.7
1	0	1	144.4 ± 6.4	265.2 ± 8.0	358.7 ± 7.1	402.9 ± 16.4
1	3	0.5	8.0 ± 0.4	30.5 ± 2.9	55.8 ± 3.2	63.6 ± 2.9
1	3	1	204.4 ± 11.9	295.3 ± 16.9	376.6 ± 19.4	415.1 ± 20.3
3	0	0.5	167.3 ± 3.5	341.5 ± 9.3	450.4 ± 17.8	481.5 ± 27.0
3	0	1	389.9 ± 27.2	717.3 ± 34.6	913.7 ± 45.8	977.5 ± 56.2
3	3	0.5	196.1 ± 1.7	418.3 ± 4.9	544.9 ± 8.0	583.5 ± 9.1
3	3	1	505.2 ± 26.3	946.0 ± 37.4	1202.7 ± 89.11	1300.0 ± 79.3
5	0	0.5	411.9 ± 26.3	782.1 ± 44.0	958.9 ± 62.1	996.1 ± 62.9
5	0	1	1045.5 ± 65.9	1695.7 ± 80.2	1965.0 ± 81.4	2040.3 ± 92.5
5	3	0.5	626.7 ± 37.2	1095.0 ± 57.7	1243.3 ± 41.5	1268.0 ± 31.5
5	3	1	1383.0 ± 72.9	2165.3 ± 100.9	2519.3 ± 131.0	2594.0 ± 143.1

Table 3. The Effects of Oscillatory Frequency on the Loss Tangent (tan δ) of Bioadhesive Formulations Containing Chlorhexidine (5% w/w as the Diacetate Salt)

Formulation components			Mean (± s.d.) tan δ of formulations at representative oscillatory frequencies			
Concⁿ. of HEC	Concⁿ. of PVP	Concⁿ. of PC	0.01 Hz	0.1142	0.5307	0.9478
1	0	0.5	1.97 ± 0.26	1.39 ± 0.01	0.99 ± 0.03	0.88 ± 0.01
1	0	1	0.55 ± 0.01	0.53 ± 0.01	0.46 ± 0.01	0.43 ± 0.02
1	3	0.5	1.68 ± 0.43	1.08 ± 0.04	0.82 ± 0.01	0.75 ± 0.01
1	3	1	0.54 ± 0.08	0.43 ± 0.02	0.40 ± 0.02	0.40 ± 0.01
3	0	0.5	0.82 ± 0.03	0.66 ± 0.04	0.52 ± 0.01	0.47 ± 0.01
3	0	1	0.62 ± 0.03	0.49 ± 0.01	0.40 ± 0.01	0.37 ± 0.01
3	3	0.5	0.86 ± 0.05	0.63 ± 0.01	0.48 ± 0.01	0.43 ± 0.01
3	3	1	0.68 ± 0.05	0.50 ± 0.03	0.40 ± 0.01	0.37 ± 0.01
5	0	0.5	0.79 ± 0.04	0.53 ± 0.01	0.40 ± 0.01	0.36 ± 0.01
5	0	1	0.60 ± 0.01	0.44 ± 0.01	0.34 ± 0.01	0.31 ± 0.01
5	3	0.5	0.75 ± 0.06	0.49 ± 0.01	0.36 ± 0.01	0.32 ± 0.01
5	3	1	0.61 ± 0.02	0.42 ± 0.01	0.30 ± 0.00	0.28 ± 0.00

and G″ of each formulation increased over the examined range of oscillatory frequency, the extent of these increases were relatively small, indicating that G′ and G″ were relatively unaffected by (i.e. poor functions of) oscillatory frequency (9). For example, in many cases G′ and G″ increased by less than one log cycle over a two cycle increase in oscillatory frequency. These observations would suggest the presence of an apparent "plateau region of viscoelasticity" in each formulation. The presence of the "plateau region" has been reported to occur in either highly cross-linked or alternatively high molecular weight uncross-linked polymeric systems (15), the structured nature of these systems preventing polymer chain rearrangements following exposure to a range of oscillatory frequencies. The characteristic response of both moduli to oscillatory frequency is indicative of the presence of a gel-like structure (9). The plateau region of viscoelasticity has been reported for other pharmaceutical semi-solids, including creams (13) and gels composed of polyacrylic acid derivatives (10), xanthan gum (9) and various cellulose polymers (5). From the observations in this current study, and from a previous study (5), it is likely that the oscillatory responses of the current formulations are a result of both their primarily uncross-linked nature and also the high molecular weight of the polymeric components.

The formulations under examination in this study have previously been characterised in terms of continuous shear (flow) rheometry and textural (mechanical) analysis (4). In this, it was shown that the state of each polymeric component within each formulation, namely whether dissolved or dispersed (with respect to HEC and PVP) and swollen or unswollen (PC), significantly affected both their mechanical and flow properties. In these formulations, HEC (1, 3, 5% w/w) was dissolved to form the primary gel. When required, PVP was then added into this gel and dissolved until saturation solubility was attained. Further additions of this polymer produced a two phase system composed of a gel state (containing dissolved HEC and PVP) and a solid, suspended state containing undissolved PVP. Following incorporation, PC did not dissolve but instead exhibited swelling (due to its cross-linked structure), the extent of which was dependent on the amount of "free" water within the formulation, i.e. water not associated with dissolved polymer (4). Similarly, in this current study, the state of each polymeric component significantly affected the structural (viscoelastic) properties of each formulation.

As the concentrations of HEC and PVP were increased, G′ and G″ of each formulation significantly increased. This may be explained by increased entanglement/interactions of

Table 4. The Effects of Oscillatory Frequency on the Dynamic Viscosity (η′) of Bioadhesive Formulations Containing Chlorhexidine (5% w/w as the Diacetate Salt)

Formulation components			Mean (± s.d.) η′ (Pa.s) of formulations at representative oscillatory frequencies			
Concⁿ. of HEC	Concⁿ. of PVP	Concⁿ. of PC	0.01 Hz	0.1142 Hz	0.5307 Hz	0.9478 Hz
1	0	0.5	47.3 ± 3.4	20.1 ± 1.4	9.3 ± 0.4	6.5 ± 0.1
1	0	1	2297.7 ± 102.5	369.6 ± 11.2	107.6 ± 2.1	67.7 ± 2.8
1	3	0.5	126.8 ± 6.6	42.5 ± 2.0	16.7 ± 1.0	10.7 ± 0.5
1	3	1	3253.0 ± 149.1	411.5 ± 27.9	112.9 ± 6.0	69.7 ± 4.0
3	0	0.5	2663.3 ± 55.9	475.9 ± 13.0	135.0 ± 5.3	80.9 ± 4.5
3	0	1	6205.3 ± 250.6	999.8 ± 30.2	274.0 ± 16.8	164.2 ± 11.5
3	3	0.5	3121.3 ± 21.8	582.8 ± 6.9	163.4 ± 2.4	98.0 ± 1.5
3	3	1	8040.3 ± 395.9	1318.7 ± 46.1	360.7 ± 21.7	218.3 ± 11.1
5	0	0.5	6556.3 ± 236.9	1089.8 ± 47.0	287.6 ± 13.7	167.3 ± 5.5
5	0	1	16633.3 ± 680.9	2363.0 ± 165.2	589.3 ± 34.5	342.6 ± 15.6
5	3	0.5	9976.3 ± 412.6	1525.7 ± 60.8	372.9 ± 12.5	212.0 ± 5.3
5	3	1	22013.3 ± 1049.6	3017.3 ± 180.1	755.5 ± 41.2	435.6 ± 25.7

polymer chains in formulations containing 1% HEC and 3% PVP and also 3% HEC and 3% PVP, in which both of these polymeric components were totally dissolved. These physical phenonmena have been previously reported for gels composed of HEC, sodium carboxymethylcellulose (5), hydroxypropylmethylcellulose or xanthan gum (9). As the saturation solubility of PVP was exceeded, i.e. in gels containing 5% HEC, further additions of PVP and PC resulted in greater masses of suspended solids, and hence the formulations adopted increasingly semi-solid (elastic) character. In these formulations, the magnitude of increase of G′ exceeded that for G″ (i.e. tan δ decreased), further illustrating the shift towards greater elastic character. In formulations containing 1% or 3% w/w HEC, 0% PVP and 0.5% w/w PC sufficient "free" water was available to allow extensive swelling of PC. This swelling resulted in an increased G′ due to the (restrained) extension of cross-linked polyacrylic acid chains (10). Increasing the concentration of PC increased product G′ and G″ due to both the greater mass of swollen polymers (in formulations containing lower concentrations of HEC, i.e. 1 and 3% and 0 or 3 % PVP) and hence greater polymer chain entanglement density, and also the greater mass of unswollen (non-neutralised) particles of this polymer. Formulations containing 5% HEC, 3% PVP and either 0.5 or 1% PC, possessed significant elasticity that may be ascribed to both the elastic network of dissolved HEC (and PVP) but, importantly, to the large mass of unswollen, i.e. suspended solid, particles of both PVP and PC. Interestingly, whilst the viscoelastic properties of these formulations offer enhanced mucoadhesion and greater prolonged drug release, their textural properties, particularly hardness, cohesiveness and spreadibility, were unacceptable for topical application (4). Again, the increasingly semisolid nature of the formulations under examination was evident from the marked decrease in tan δ. Whilst most formulations exhibited predominantly elastic behaviour, i.e. tan $\delta < 1$, there were however two noticable exceptions, namely formulations containing 1% HEC, 0. 5% PC and either 0% or 3% PVP, which displayed predominatly viscous behaviour at lower oscillatory frequencies (tan $\delta > 1$). It would be expected that the structural (viscous) properties of these formulations would be inappropriate for clinical application due to their susceptibility to structural deformation (and hence removal) following application of shear stresses within the oropharynx.

The dynamic viscosity of each formulation was observed to be dependent on the oscillatory frequency, in accordance with the Maxwell model of viscoelasticity. Hence, at large oscillatory frequencies, the elastic properties of the formulations dominate whereas, at lower frequencies, the viscous contributions to the viscoelastic properties predominate. The dynamic viscosity (G''/ω) is commonly employed to characterise the viscous nature of viscoelastic systems (14,16), primarily liquids, and consequently, the magnitude of η' will decrease as the oscillatory frequency increases, i.e. shear-thinning under an oscillatory stress. Increasing concentrations of each polymeric component significantly increased η', reflecting the effects of each polymeric component on the overall viscosity of each formulation, as previously reported by us (4).

The statistical interactions observed in the factorial analysis between the effects of HEC and PC and between HEC and PVP with respect to G′, G″, tan δ and η' may be assigned to the effects of HEC on the physical states of PVP (dissolved/dispersed) and PC (swollen/unswollen), as fully described in a previous publication (4). Hence, formulations containing 5% HEC possessed the greatest mass of undissolved PVP and unswollen PC, resulting in a dramatic increase in the semi-solid nature and hence the unpredicted effects on viscoelastic behaviour, namely increased G′, G″, η' and decreased tan δ. In formulations containing the lower concentrations of HEC, the mass of suspended polymers was decreased and hence the effects on the viscoelastic parameters were not as marked. These apparent (formulation dependent) disparities accounted for the observed statistical interactions.

Following application to the oropharynx, it is anticipated that the formulations will encounter a wide range of non-destructive shearing stresses associated with normal physiological functions. Little information is available concerning the shear rate associated with physiological functions within the oropharynx, however, one study reported that the oscillatory rate associated with ciliary movement was approximately 0.5–3.0 Hz (17). Within this approximate frequency range, the formulations under examination behaved primarily as elastic systems. As a consequence, their clinical performance will be directly affected by their specific viscoelastic character. For example, increased polymeric entanglement (and hence increased elasticity) has been observed to decrease the rate of drug release from semi-solid formulations (18), an advantageous property for the formulations under examination. Furthermore, it has been reported that the bioadhesion of gel formulations increases as their relative elastic properties increase, i.e. tan δ decreases (5,7). Therefore, to ensure prolonged retention within, and prolonged drug release into the oropharynx, formulations should be chosen that exhibit elastic properties under the conditions of oscillatory stresses operative at the site of application. In light of the consistency of viscoelastic response of the majority of formulations over the range of oscillatory frequencies that may be anticipated in vivo, these formulations would be expected to exhibit uniform rheological properties, and hence uniform clinical performance following topical application.

In conclusion, the viscoelastic properties of bioadhesive, chlorhexidine-containing semi-solids designed for topical application to the oropharnx have been examined using oscillatory rheometry. Previous studies have identified the possible clinical benefits of formulation elasticity (structure) in the processes of bioadhesion and drug release (5,7,18). To this end, formulations containing 5% HEC, 3% PVP and 1% PC and chlorhexidine (5% w/w, as the diacetate) were shown to possess both the greatest elastic character (lowest tan δ), lowest release rates and also the greatest adhesiveness, a parameter related to bioadhesion (5), in textural analysis (4). However, these formulations also displayed inappropriate spreading, cohesiveness and hardness properties for use as topical formulations (4) and therefore would be clinical unacceptable to patients. Conversely, the viscoelastic properties of formulations containing 1% HEC, 0 or 3% PVP and 0.5 or 1% PC were relatively intolerant to oscillatory frequency, exhibited poor elasticity and thus would be expected to exhibit variable performance in vivo. Therefore these formulations are inapropriate for clinical use. Therefore, in the choice of candidate formulations for clinical investigation, a compromise is required between acceptable textural and viscoelastic properties. In this current study, these requirements are optimally fulfilled by formulations containing 3% HEC, PVP (0 or 3% w/w) and 0.5 or 1% PC. These formulations were tolerant of the range of oscillatory frequencies expected in vivo and, additionally, exhibited acceptable textural and viscoelastic

properties, the latter ensuring acceptable drug release and bioadhesive characteristics.

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