Textural Analysis and Flow Rheometry of Novel, Bioadhesive Antimicrobial Oral Gels

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Received October 29, 1996; accepted January 21, 1997

Purpose. This study examined the rheological and textural characteristics (hardness, compressibilty, adhesiveness and cohesiveness) of bioadhesive oral gels containing the antimicrobial agent chlorhexidine.
Methods. Textural analysis was performed using a Stable Micro Systems texture analyser (model TA-XT 2) in texture profile analysis (TPA) mode. In this, an analytical probe was twice compressed into each formulation to a defined depth (15 mm) and at defined rates (2, 4, 6, 8, 10 mm s^{-1}), allowing a delay period (15 s) between the end of the first and beginning of the second compressions. Flow rheograms were performed using a Carri-Med CSL^2-100 rheometer with parallel plate geometry under controlled shearing stresses at 20.0 ± 0.1°C.
Results. All formulations exhibited pseudoplastic flow with thixotropy. Increasing concentrations of each polymer significantly increased formulation hardness, compressibility, adhesiveness and zero-rate viscosity. Increased hardness and compressibility were due to the attendent increased viscosities of these formulations. Increased adhesiveness was related to the concentrations of the (bioadhesive) polymers employed in these formulations and, in addition, was dependent on the physical state of polycarbophil. Formulation viscosity contributed to product adhesiveness, reflecting the importance of product rheology on this parameter. Decreased formulation cohesiveness, observed as the concentrations of the PVP, PC and HEC (3–5%w/w) were increased, was due an increase in semi-solid character. Numerical values of hardness, compressibility and adhesiveness were affected by the choice of probe speed, a parameter related to rate of shear in flow rheometry. Statistical interactions were observed and were assigned to the effects of HEC on the physical state of PVP (dissolved or dispersed) and PC (swollen or unswollen).
Conclusions. This study has demonstrated both the applicability of textural analysis for the mechanical characterisation of bioadhesive semi-solid gel systems and, additionally, the direct influence of viscosity on the parameters defined by textural analysis, namely, hardness, compressibility and adhesiveness.

KEY WORDS: texture profile analysis; bioadhesion; semi-solids; hardness; compressibility; adhesiveness; cohesiveness; flow rheometry.

INTRODUCTION

The use of topical antimicrobial agents for the treatment and prophylaxis of infection within the oral cavity is generally preferred, as this allows direct access of high local concentrations of antimicrobial agents to pathogenic micro-organisms (1). However, the duration of antimicrobial effect of topically-applied formulations is short due to the poor retention of the delivery system within the oral cavity (2,3,4). The retention of antimicrobial agents within the oral cavity may be influenced by both the type and formulation of the delivery system (5,6). Aqueous-based systems, e.g., mouthwashes, suspensions, aerosols, are convenient to use but exhibit poor retention within the oral cavity. Non-aqueous systems, e.g., ointments, paints/varnishes, show superior retention characteristics. However, they are frequently disadvantaged by either poor "mouth-feel" characteristics or by the requirement for application by trained personnel (1).

It has been suggested that the delivery of antimicrobial drugs to the oral cavity may be improved by the incorporation of bioadhesive polymers as fundamental components of the delivery system (7). Bioadhesive polymers characteristically show adhesive interactions with a biological membrane, either in the presence (e.g. the oral cavity) or absence of mucus. Therefore, such polymers may be utilised to "anchor" the formulation to the oral mucosae, allowing subsequent controlled release of the drug.

Formulations which have been designed for topical application to the oral cavity must exhibit acceptable mechanical characteristics, e.g., ease of application, low hardness, good retention at the site of application. One method by which the mechanical properties of polymeric systems may be conveniently determined is texture profile analysis. (8). In this, an analytical probe is twice depressed into the sample at a defined rate to a desired depth, allowing a pre-defined recovery period between the end of the first and the beginning of the second compressions. From the resultant force-time curve (Figure 1) the following mechanical parameters may be derived (8,9,10);

- hardness (force required to attain a given deformation)
- compressibility (the work required to deform the product during the first compression cycle of the probe)
- adhesiveness (the work necessary to overcome the attractive forces between the surface of the product and the surface of the probe with which the sample comes into contact)
- cohesiveness (the ratio of the area under the force-time curve produced on the second compression cycle to the corresponding area produced on the first compression cycle).

Recently, we described the formulation of bioadhesive semi-solids containing tetracycline designed for the treatment of periodontits. These were designed to exhibit controlled drug release, good retention within the periodontal pocket and to be directly applied into the periodontal pocket using a periodontal syringe (8,11). Using a related formulation strategy, this study describes the design, characterisation and selection of bioadhesive semi-solid systems containing chlorhexidine (as a model antimicrobial agent) for topical application to the oral cavity using texture profile analysis. This analytical technique is particularly useful for this purpose as the mechanical properties derived from TPA are directly relevant to clinical practice. Hence, formulation compressibility and hardness are related to ease of product removal from a container, ease of application onto a substrate and product comfort within the oral cavity, whereas, adhesiveness, a property related to bioadhesion, describes the relative adhesive properties of each candidate formulation. TPA also provides information on the effects of

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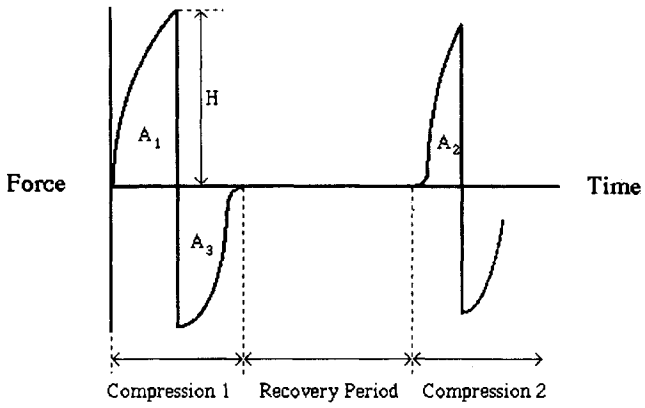

H = Hardness
A_1 = Compressibility
A_3 = Adhesiveness
A_2 / A_1 = Cohesiveness

Fig. 1. Graphical output from Texture Profile Analysis. The ordinate axis (time) may be converted into distance for the determination of work done by the probe in either compression or tension modes.

repeated shearing stresses on the structural properties of formulations (cohesiveness). In addition, rheological performance was also determined using flow rheometry to quantify both the general rheological properties of the candidate formulations and also to evaluate the contribution of viscosity to textural characteristics

MATERIALS AND METHODS

Materials

Hydroxyethylcellulose (Natrosol 250 HHX-Pharm), polyvinylpyrrolidone K90 F and polycarbophil (Noveon AA-1) were gifts from Aqualon Ltd. (Warrington, UK), BASF (Ludwigshafen, Germany) and B.F. Goodrich Company (Cleveland, Ohio, USA), respectively. Chlorhexidine (as the diacetate salt) was purchased from BDH Laboratory Supplies, Poole, UK. All other chemicals were purchased from Sigma Chemical Co., (St. Louis, USA) and were of AnalaR, or equivalent, grade.

Manufacture of Bioadhesive Formulations Containing Chlorhexidine

Hydroxyethylcellulose (HEC; 1, 3 or 5% w/w) was initially dissolved using a mechanical (Heidolph) stirrer (1000 rev min^{-1}) in the required amount of phosphate buffered saline (PBS, 0.03M, pH 6.8). This pH value was selected to avoid the possible cariogenic effects associated with acidic formulations. The gel was then transferred onto an ointment slab and into this polyvinylpyrrolidone (PVP; 3% w/w), when required, and polycarbophil (PC; 0.5, 1.0% w/w) were thoroughly dispersed. Finally, chlorhexidine (5% w/w, as the diacetate salt, particle size <63μm) was thoroughly mixed into the semi-solid formulations until homogeneous. All formulations were placed in a vacuum, to ensure removal of entrapped air, and stored at 4°C for 14 days prior to analysis.

Mechanical Characterisation of Bioadhesive, Chlorhexidine-Containing Formulations Using Texture Profile Analysis

Texture profile analysis (TPA) was performed using a Stable Micro Systems Texture Analyser (Model TA-XT2) as previously described (8,9,10,12). Formulations were carefully transferred into McCartney bottles (of identical dimensions), packed to a fixed height (7 cm) avoiding the introduction of air into the samples and the temperature of each allowed to equilibrate to 20 ± 1°C by storage in an oven for 48 hours. In TPA the analytical polycarbonate probe (10 mm diameter) was compressed twice into each sample to a depth of 15 mm at pre-defined rates (2.0, 4.0, 6.0, 8.0, 10.0 mm s^{-1}), allowing a delay period of 15 s between the end of the first and the beginning of the second compression. At least four replicate analyses were performed for each formulation at ambient temperature (circa 20°C) using a fresh sample in each case.

Rheological Analysis of Semi-Solid Formulations

Flow curves (rheograms) of each formulation under examination were performed at 20 ± 0.1°C using a Carri-Med CSL^2-100 rheometer in flow mode in conjunction with parallel plate (2 cm) geometry separated by a fixed distance (1.0 mm). Samples were applied to the lower plate using a spatula to ensure that formulation shearing did not occur. Rheograms were produced (at least in duplicate) under controlled stress by gradually increasing the shearing stress using the following regimens:

1. from 50 Pa to 175 Pa in 60 s, followed by 10 s delay at 175 Pa and then from 175 Pa to 50 Pa in 60 s, employed for formulations containing 1% w/w HEC.
2. from 500 Pa to 1000 Pa in 60 s, followed by 10 s delay at 1000 Pa and then from 1000 Pa to 500 Pa in 60 s, employed for formulations containing 3% w/w HEC.
3. from 1000 Pa to 2000 Pa in 60 s, followed by 10 s delay at 2000 Pa and then from 2000 Pa to 1000 Pa in 60 s, employed for formulations containing %% w/w HEC.

The ranges of shearing stresses employed were selected according to the consistencies of each formulation (13). The zero-rate viscosity of each formulation was derived from the flow curves using the Cross Model, as previously reported (14).

Statistical Analysis

The effects of HEC, PVP and PC and analytical probe speed on formulation hardness, compressibility, adhesiveness and cohesiveness were statistically evaluated using a four-way analysis of variance (ANOVA) (12). Additionally, the effect of each polymeric component on the zero-rate viscosity of each formulation were evaluated using a three-way ANOVA. Post-hoc statistical comparisons of the means of individual groups was performed using Scheffe's test. In all analyses, $P < 0.05$ denoted significance.

RESULTS

The formulations in this study (Table 1) exhibited a wide range of mechanical and rheological properties. The effects of HEC, PVP and PC on the hardness, compressibility and adhesiveness, as determined using TPA over the selected range

Table 1. Formulations of Bioadhesive Oral, Topical Formulations Containing Chlorhexidine (5% w/w, as the diacetate), as Used in the Study

Formulation	HEC% w/w	PVP% w/w	PC% w/w
A	1	0	0.5
B	1	0	1
C	1	3	0.5
D	1	3	1
E	3	0	0.5
F	3	0	1
G	3	3	0.5
H	3	3	1
I	5	0	0.5
J	5	0	1
K	5	3	0.5
L	5	3	1

of probe speeds, are presented in Table 2. Raising concentrations of HEC (from 1–3% and from 3–5% w/w), PVP (from 0–3% w/w) and/or PC (from 0.5–1% w/w) significantly increased formulation hardness, the work required for product compression (compressibility) and adhesiveness. Minimum and maximum hardness, compressibility and adhesiveness were exhibited by formulations containing HEC 1% w/w, PVP 0% w/w, PC 0.5% w/w and HEC 5% w/w, PVP 3% w/w, PC 1% w/w, respectively. Product cohesiveness was significantly affected by each polymeric constituent. Increasing the concentration of HEC from 1% to 3% w/w significantly increased product cohesiveness, yet a further increase in concentration from 3% to 5% w/w had the opposite effect. The effect of PVP on product cohesiveness was dependent on the concentration of HEC. Thus, in the presence of 1% w/w HEC, increasing the concentration of PVP from 0% to 3% w/w significantly increased cohesiveness, whereas in the presence of 3% or 5% w/w HEC, PVP significantly reduced product cohesiveness. The effects of PC on formulation cohesiveness was dependent on the concentrations of both HEC and PVP. In formulations containing 3% PVP and 1% HEC increasing the concentration of PC from 0.5% to 1% w/w significantly increased product cohesiveness. However, formulations containing either 3% or 5% w/w HEC and 3% PVP exhibited significantly reduced cohesiveness in comparison to similar formulations devoid of PVP. These apparent disparities were highlighted as statistically significant interactions between HEC and PVP and between HEC and PC in the ANOVA. Additionally, other significant statistical interactions were observed between HEC and PVP, and between HEC and PC with respect to product hardness, compressibility and adhesiveness. These may be explained by the significantly greater numerical values of these parameters in the presence of 5% w/w HEC compared to values obtained in the presence of lower concentrations of this polymer.

The rate of formulation deformation (probe speed) significantly affected the numerical values of hardness, compressibility and adhesiveness. In these, increasing probe speed significantly increased numerical values of these mechanical parameters. Overall, probe speed did not significantly alter numerical values of cohesiveness ($p > 0.05$). However, post-hoc statistical analysis (Scheffe's test) revealed that increased probe speed significantly increased formulation cohesiveness (only) in formulations containing 1% w/w HEC,.

Figures 2, 3 and 4 are the flow curves for formulations containing 1% w/w, 3% w/w and 5% w/w HEC, respectively, in addition to PVP (0, 3% w/w) and PC (0.5% 1% w/w). All formulations demonstrated pseudoplastic flow with thixotropy. Increasing the concentrations of each polymeric component significantly increased the zero-rate viscosity of each formulation. A summary of the zero-rate viscosities obtained is presented in Table 3. Statistical interactions were observed between the effects of each polymeric constituent on zero-rate viscosity, i.e. between HEC and PVP, between HEC and PC and between PVP and PC. In these, the effects of PVP and PC on the apparent viscosities of formulations containing 5% w/w HEC were significantly greater than in formulations containing 3% and 1% HEC. Similarly, the effects of these polymers on formulations containing 3% HEC were significantly greater than in formulations containing 1% HEC.

DISCUSSION

The design and development of topical formulations designed for prolonged application to the oral cavity presents a special challenge to the pharmaceutical formulator. Several desirable formulation attributes may be defined, including ease of removal of the product from the container, favourable spreading characteristics over, and prolonged adhesion to, the mucosal epithelium and reformation of the structural characteristics of the formulations following application. However, there are few analytical techniques which can conveniently assess and measure these parameters. More recently, we have described the use of texture profile analysis for the characterisation of pharmaceutical semi-solids (8,12). Importantly, the information derived from TPA is appropriate for the development of topical formulations as it describes the mechanical properties in terms of hardness and compressibility, factors which have been reported to affect both the ease of removal of the product from the container, the spreadability of the product on a substrate and also the perceived "mouth-feel" of the product, adhesiveness, a property related to bioadhesion (8) and finally cohesiveness, the extent of structural reformation following subsequent applications of a shearing stress. This study therefore represents the first application of TPA for the characterisation and potential selection of candidate topical formulations for application to the oral cavity.

The polymeric components employed in these formulations significantly affected the resultant mechanical and rheological properties. Therefore, it is worthwhile to reflect upon the physical state of each component within the formulation. In all formulations HEC is initially dissolved to form a primary gel. If required, PVP is dissolved into this primary gel system until its saturation solubility is achieved. Further addition of PVP results in the development of a two-phase system in which PVP is suspended in the gel base. In formulations containing 1% w/w HEC, PVP (3% w/w) was totally dissolved. However, in all other formulations PVP existed as a suspended solid. PC is an insoluble, cross-linked polyacrylic acid which exhibits swelling dependent upon the amount of free water available within the formulation. Consequently, in formulations containing 1% w/w HEC and no PVP, there is a greater amount of free water available, i.e. water not associated with dissolved HEC, and consequently, PC exhibits maximal swelling. Con-

Table 2. The Effects of Hydroxyethylcellulose, Polyvinylpyrrolidone and Polycarbophil on the Hardness, Compressibility, Adhesiveness, and Cohesiveness of Oral, Topical Formulations Containing Chlorhexidine (5% w/w, as the diacetate), as Determined Using Texture Profile Analysis

	Mean values ± s.d.				
Probe speed (mm s^{-1})	2	4	6	8	10
Formulation A					
hardness N	0.07 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.10 ± 0.00	0.11 ± 0.01
compressibility N mm	0.46 ± 0.13	0.65 ± 0.03	0.79 ± 0.10	0.93 ± 0.04	1.02 ± 0.12
adhesiveness N mm	0.19 ± 0.03	0.37 ± 0.03	0.37 ± 0.01	0.33 ± 0.05	0.36 ± 0.04
cohesiveness	0.19 ± 0.03	0.52 ± 0.04	0.66 ± 0.03	0.76 ± 0.03	0.84 ± 0.06
Formulation B					
hardness N	0.07 ± 0.00	0.102 ± 0.01	0.11 ± 0.02	0.12 ± 0.01	0.15 ± 0.02
compressibility N mm	0.48 ± 0.06	0.90 ± 0.22	0.87 ± 0.22	0.98 ± 0.09	1.41 ± 0.20
adhesiveness N mm	0.27 ± 0.07	0.37 ± 0.06	0.41 ± 0.10	0.42 ± 0.11	0.52 ± 0.10
cohesiveness	0.21 ± 0.00	0.62 ± 0.03	0.68 ± 0.05	0.75 ± 0.01	0.83 ± 0.08
Formulation C					
hardness N	0.10 ± 0.01	0.14 ± 0.01	0.16 ± 0.01	0.16 ± 0.01	0.16 ± 0.01
compressibility N mm	0.72 ± 0.06	1.20 ± 0.08	1.44 ± 0.09	1.42 ± 0.15	1.64 ± 0.13
adhesivenes N mm	0.49 ± 0.01	0.67 ± 0.06	0.82 ± 0.05	0.81 ± 0.06	0.74 ± 0.08
cohesiveness	0.57 ± 0.06	0.78 ± 0.02	0.87 ± 0.04	0.86 ± 0.01	0.87 ± 0.03
Formulation D					
hardness N	0.15 ± 0.02	0.17 ± 0.01	0.21 ± 0.02	0.21 ± 0.02	0.22 ± 0.01
compressibility N mm	0.96 ± 0.27	1.26 ± 0.01	1.66 ± 0.21	1.71 ± 0.20	1.80 ± 0.20
adhesiveness N mm	0.79 ± 0.12	0.96 ± 0.07	1.11 ± 0.15	1.11 ± 0.13	1.12 ± 0.11
cohesiveness	0.76 ± 0.01	0.85 ± 0.03	0.89 ± 0.02	0.93 ± 0.02	0.96 ± 0.02
Formulation E					
hardness N	0.70 ± 0.06	0.88 ± 0.07	0.92 ± 0.01	0.95 ± 0.04	0.97 ± 0.07
compressibility N mm	5.78 ± 0.48	7.82 ± 0.69	8.39 ± 0.48	8.70 ± 0.05	9.41 ± 0.73
adhesiveness N mm	4.12 ± 0.33	5.37 ± 0.48	5.50 ± 0.09	5.57 ± 0.23	6.04 ± 0.51
cohesiveness	0.94 ± 0.02	0.94 ± 0.04	0.95 ± 0.02	0.94 ± 0.04	0.96 ± 0.00
Formulation F					
hardness N	0.96 ± 0.02	1.10 ± 0.05	1.12 ± 0.03	1.25 ± 0.04	1.38 ± 0.02
compressibility N mm	7.61 ± 0.30	9.28 ± 0.58	10.18 ± 1.07	11.29 ± 0.43	12.54 ± 0.42
adhesiveness N mm	6.21 ± 0.31	7.02 ± 0.37	7.59 ± 0.42	8.16 ± 0.55	9.20 ± 0.44
cohesiveness	0.94 ± 0.01	0.92 ± 0.02	0.92 ± 0.03	0.94 ± 0.04	0.91 ± 0.03
Formulation G					
hardness N	0.98 ± 0.05	1.14 ± 0.04	1.22 ± 0.08	1.31 ± 0.05	1.30 ± 0.06
compressibility N mm	8.35 ± 0.34	10.08 ± 0.17	11.21 ± 0.92	11.90 ± 0.44	13.02 ± 0.36
adhesiveness N mm	6.02 ± 0.22	6.85 ± 0.23	7.43 ± 0.69	7.82 ± 0.48	8.16 ± 0.39
cohesiveness	0.95 ± 0.01	0.88 ± 0.02	0.90 ± 0.00	0.92 ± 0.01	0.97 ± 0.00
Formulation H					
hardness N	1.10 ± 0.01	1.41 ± 0.03	1.56 ± 0.10	1.61 ± 0.05	1.76 ± 0.08
compressibility N mm	8.29 ± 0.53	11.57 ± 0.37	13.63 ± 1.11	14.57 ± 0.90	16.77 ± 1.11
adhesiveness N mm	6.31 ± 0.27	8.75 ± 0.06	9.33 ± 0.72	10.15 ± 0.52	10.77 ± 1.16
cohesiveness	0.88 ± 0.01	0.81 ± 0.01	0.87 ± 0.01	0.88 ± 0.01	0.89 ± 0.01
Formulation I					
hardness N	1.91 ± 0.07	2.24 ± 0.05	2.27 ± 0.02	2.49 ± 0.16	2.59 ± 0.10
compressibility N mm	16.44 ± 0.44	19.91 ± 0.95	20.67 ± 0.09	23.45 ± 1.97	25.63 ± 1.08
adhesiveness N mm	10.77 ± 1.04	12.71 ± 1.21	12.73 ± 0.67	14.06 ± 1.56	15.15 ± 0.51
cohesiveness	0.83 ± 0.05	0.79 ± 0.02	0.80 ± 0.04	0.80 ± 0.05	0.77 ± 0.09
Formulation J					
hardness N	2.21 ± 0.138	2.47 ± 0.12	2.75 ± 0.09	2.95 ± 0.09	3.09 ± 0.08
compressibility N mm	18.03 ± 1.72	20.87 ± 1.59	24.81 ± 1.12	27.49 ± 1.43	30.40 ± 1.13
adhesiveness N mm	13.08 ± 1.32	13.91 ± 1.66	16.19 ± 0.51	17.13 ± 0.95	18.11 ± 1.03
cohesiveness	0.84 ± 0.00	0.79 ± 0.02	0.79 ± 0.04	0.80 ± 0.03	0.74 ± 0.02
Formulation K					
hardness N	2.85 ± 0.19	3.19 ± 0.21	3.42 ± 0.10	3.68 ± 0.15	3.73 ± 0.16
compressibility N mm	24.78 ± 1.28	28.38 ± 1.93	30.82 ± 2.72	34.71 ± 1.67	36.04 ± 1.79
adhesiveness N mm	15.68 ± 0.82	16.74 ± 1.98	18.72 ± 0.17	19.65 ± 1.58	19.71 ± 1.21
cohesiveness	0.77 ± 0.02	0.76 ± 0.01	0.78 ± 0.01	0.78 ± 0.01	0.76 ± 0.00
Formulation L					
hardness N	3.09 ± 0.12	3.62 ± 0.10	3.77 ± 0.15	4.04 ± 0.09	4.30 ± 0.11
compressibility N mm	25.02 ± 2.36	31.66 ± 1.45	33.11 ± 3.41	37.23 ± 1.49	43.04 ± 1.84
adhesiveness N mm	17.45 ± 2.03	20.51 ± 1.01	21.40 ± 1.28	22.47 ± 2.41	23.57 ± 0.69
cohesiveness	0.77 ± 0.02	0.73 ± 0.01	0.74 ± 0.02	0.75 ± 0.00	0.75 ± 0.01

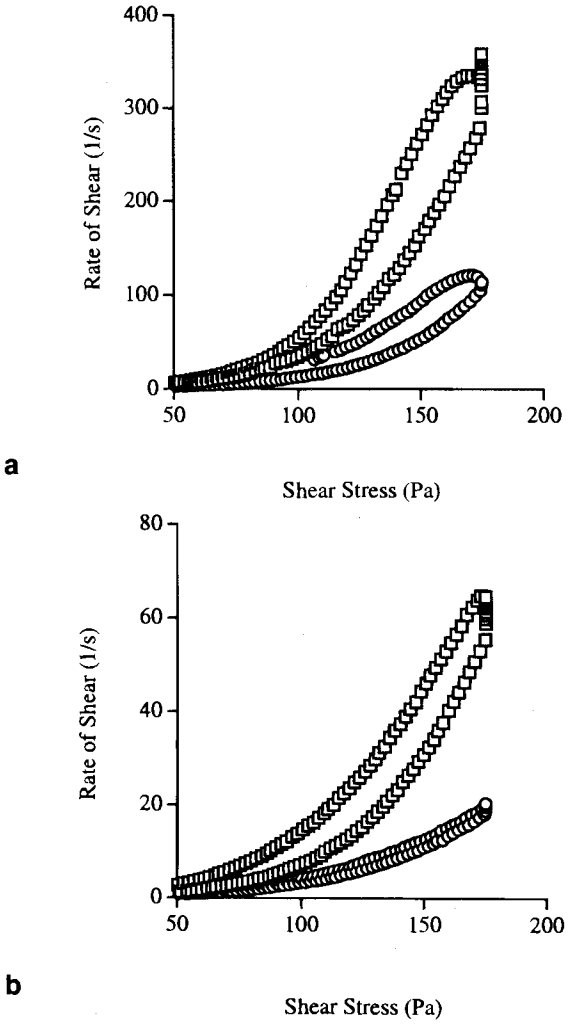

Fig. 2. Flow curves for formulations containing 1% HEC. Figure 2a depicts the flow curves for formulations containing 0% w/w PVP and either 0.5% w/w PC(squares) or 1% w/w PC (circles). Figure 2b depicts the flow curves for formulations containing 3% w/w PVP and either 0.5% w/w PC (squares) or 1% w/w PC (circles). Each datum point is the mean of at least duplicate analyses. Error bars have been omitted to retain clarity, however, in all cases the coefficient of variation of replicate analyses was less than 5%.

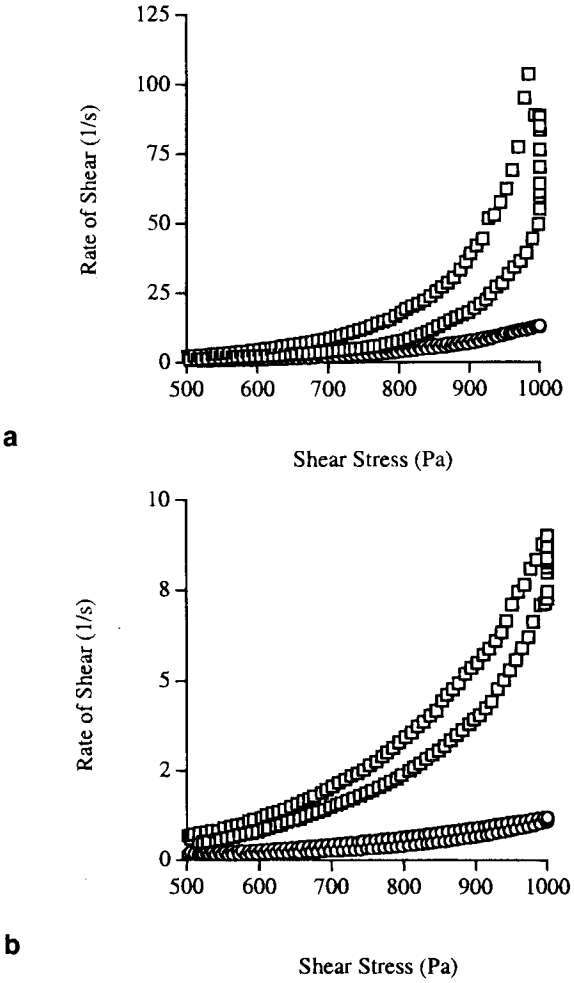

Fig. 3. Flow curves for formulations containing 3% HEC. Figure 3a depicts the flow curves for formulations containing 0% w/w PVP and either 0.5% w/w PC(squares) or 1% w/w PC (circles). Figure 3b depicts the flow curves for formulations containing 3% w/w PVP and either 0.5% w/w PC (squares) or 1% w/w PC (circles). Each datum point is the mean of at least duplicate analyses. Error bars have been omitted to retain clarity, however, in all cases the coefficient of variation of replicate analyses was less than 5%.

versely, in formulations containing 5% w/w HEC, PVP 3% w/w and 1% w/w PC, a large percentage of PC exists in the formulation as a suspended, unswollen solid due to the relative sparsity of available water. Furthermore, in formulations containing 3% w/w PC, a greater percentage of this polymer will exist as unswollen solid material in comparison to formulations containing the lower concentration of this polymer (1% w/w). It is proposed that the states of these polymeric components within each formulation, i.e. dissolved or dispersed (with respect to PVP) and swollen/unswollen (with respect to PC), are directly responsible for the resultant mechanical and rheological properties.

Product hardness and compressibility, parameters which are components of shearing stress, were dependent on the concentrations of HEC, PVP and PC. There have been a limited number of studies which have addressed the effects of formulation components on product compression characteristics. Recently, Ferrari *et al.* (15) reported that the gel strength of hydroxypropylmethylcellulose gels increased as their concentrations increased whereas McTaggart and Halbert (16) related increased gel hardness to degree of cross-linking. In addition, Lucero *et al.* (17,18) have described the effects of antioxidants (ascorbic acid, butylhydroxytoluene) and α-tocopherol on the spreadability of gel-based formulations. Increased concentrations of each of the polymeric components used in the current study increased overall formulation consistencies, as observed by the increased zero-rate viscosities. Furthermore, correlations were observed between increased formulation viscosity and increased product hardness and compressibility, reflecting the importance of viscosity on these compression characteristics. Therefore, the effects of HEC, PVP and PC on the hardness and compressibility of the semi-solid formulations under examination are a direct consequence of the viscosity enhancing effects of these polymers, either following dissolution or as dispersed, swollen or unswollen solids. Increased product viscosity will offer an increased resistance to product deformation in TPA and therefore increased product hardness and force per

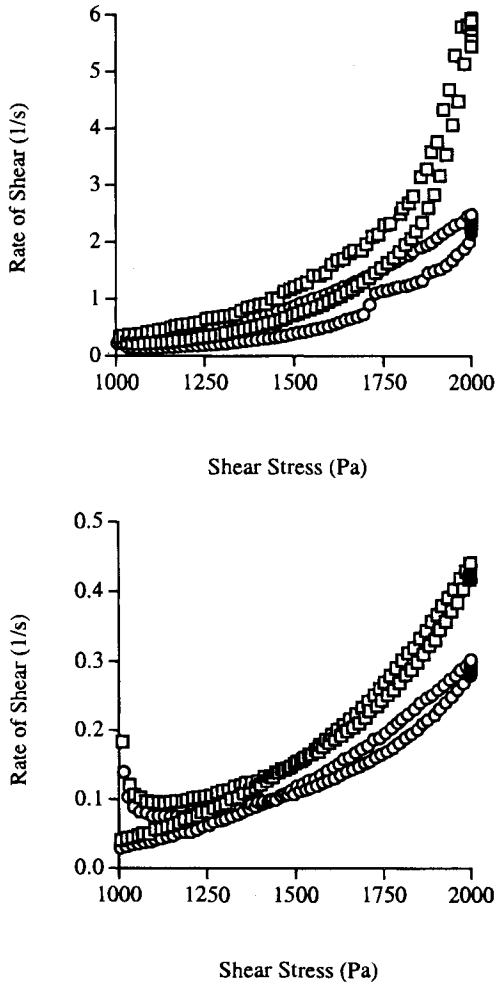

Fig. 4. Flow curves for formulations containing 5% HEC. Figure 4a depicts the flow curves for formulations containing 0% w/w PVP and either 0.5% w/w PC(squares) or 1% w/w PC (circles). Figure 4b depicts the flow curves for formulations containing 3% w/w PVP and either 0.5% w/w PC (squares) or 1% w/w PC (circles). Each datum point is the mean of at least duplicate analyses. Error bars have been omitted to retain clarity, however, in all cases the coefficient of variation of replicate analyses was less than 5%.

unit time required for product compression will result. Similarly, Lucero *et al.* (18) reported a correlation between apparent viscosity and spreadability of gel formulations. The observed statistical interactions are attributed to the greater effects of PVP and PC on hardness, compressibility and zero-rate viscosity in the presence of HEC 5% w/w in comparison to the lower concentrations of this polymer. These interactions provide a further insight to the effects of the physical state of PVP and PC in each formulation. As the concentration of HEC increases, PVP and PC exist increasingly as dispersed (unswollen) solids. It is the greater mass of suspended solids which is responsible for the unexpectedly significant increases in product hardness, compressibility and apparent viscositites associated with formulations containing 5% w/w HEC. The rheograms of each formulation were pseudoplastic with thixotropy. Therefore, following application of shearing stresses of increasing magnitudes, there was a general loss in the consistency of each formulation, i.e. shear thinning. This property would be expected to be advantageous whenever the formulations are applied to the oral cavity.

Formulations that have been designed for topical use in the oral cavity should exhibit adhesion to mucosal surfaces, as this will decrease their clearance time and, hence, improve clinical efficacy. The polymers examined in this investigation have been described as bioadhesive and, therefore, will interact with the appropriate substrate to locate the formulation at the site of application (7,19). In TPA, adhesiveness is defined as the work required to overcome the attractive forces between the surface of the sample and the surface of the probe (8,10), and is derived from the area under the force-time curve during the tension phase of TPA. Therefore, adhesiveness may, more correctly, represents the work required to remove the probe from the sample, inferring that for some samples probe removal may occur following cleavage of both internal bonds within the sample (cohesive bonds) and also bonds occurring between the sample and the surface of the probe (adhesive bonds). Increased formulation adhesiveness due to increased concentrations of HEC, PVP or PC may be attributed both to the increased ability of these polymers to chemically interact with the analytical probe and may also be a function of the increased tack of each formulation. The bioadhesion of PC has been reported to be affected by the number of free (uncharged) carboxylic acid groups present on the polymer chains (7) and similarly this has been reported to affect formulation adhesiveness in TPA (8). Consequently in formulations containing 3% PC, a greater mass of unswollen (and hence unneutralised) particles will exist in comparison to formulations containing 1% PC. Therefore, this will account, at least in part, for the observed increase in adhesiveness. Statistical interactions were observed between HEC and PC and HEC and PVP and can also be explained by the effects of the state of each polymeric component on formulation adhesiveness. In the presence of 5% w/w HEC and 3% w/w PVP, there is a relatively lower amount of free water available in the formulation and PC will therefore exist primarily as an unswollen, uncharged solid which exhibits maximum adhesiveness. In formulations containing 1% w/w HEC and PVP (either 0 or 3% w/w), there is sufficient free water to permit neutralisation of PC to proceed, with resultant swelling. The adhesiveness of formulations in which PC undergoes swelling will be markedly reduced in comparison to those in which PC exists as a suspended solid (7,8).

Product cohesiveness describes the extent of structural reformation following successive compressions. Increased concentrations of each polymeric component significantly affected product cohesiveness. Decreased product cohesiveness following increased concentrations of HEC (from 3–5% w/w), PVP (0–3% w/w) and/or PC (0.5–1% w/w) may be explained by both the greater masses of suspended solids present, which will alter the structural properties of the formulations, and also by the effects of these polymers on the overall viscosity, as this will affect the viscoelastic properties of the formulations. Paradoxically, raising the concentrations of PVP and PC increased the cohesiveness of products containing 1% HEC. In these formulations, the first compression of the probe into the samples was sufficient to markedly alter their structural properties. Therefore, due to these effects, the work required to compress the sample on the second compression cycle was reduced and consequently the cohesiveness (the ratio between the work required to compress the sample on the second compression cycle to that on the first) was also reduced. As the concentrations

Table 3. The Effects of Hydroxyethylcellulose, Polyvinylpyrrolidone and Polycarbophil on the Zero-Rate Viscosities of Oral, Topical Formulations Containing Chlorhexidine (5% w/w, as the Diacetate)

Mean (± s.d.) zero-rate viscosities[a] (Pa·s) of formulations containing				
Conc[a] of polyvinylpyrrolidone (% w/w)	Conc[a] of polycarbophil (% w/w)	Hydroxyethylcellulose (1% w/w)	Hydroxyethylcellulose (3% w/w)	Hydroxyethylcellulose (5% w/w)
0	0.5	44.3 ± 0.8	1350.0 ± 59.8	13235.5 ± 20.5
0	1.0	48.8 ± 0.7	3059.0 ± 201.4	17285.0 ± 625.2
3	0.5	118.6 ± 2.8	6288.2 ± 450.6	18960.2 ± 196.5
3	1.0	178.4 ± 10.0	9687.4 ± 100.6	24950.0 ± 625.3

[a] Calculated using the Cross Model as described in materials and methods.

of PVP and PC were increased in gels containing 1% w/w HEC, the gel structure was more coherent and hence the cohesiveness increased. Once more the interaction terms observed in the statistical analysis may be explained by the unexpectedly large decrease in cohesiveness observed for formulations containing 5% w/w HEC and, additionally, the increased cohesiveness in formulations containing 1% w/w HEC following inclusion of greater masses of PVP and/or PC.

In this study, the numerical descriptions of hardness, compressibility and adhesiveness, but not cohesiveness (as this value is a ratio) were significantly influenced by the choice of probe speed used in TPA. Previously, Ferrari *et al.* (15) observed that the numerical description of gel strength, as determined using a compression test, increased as the rate of compression increased. Therefore, as the rate of probe entry or removal is analogous to rate of shear in flow rheometry, increasing the probe speed will increase the shearing stress on the sample. Thus, the observed increased numerical values of hardness, compressibility and adhesiveness are to be expected as these parameters are components of shearing stress. In addition, the rate of probe removal from the samples will affect the rheological properties of each formulation which, given the reported importance of gel rheology on bioadhesion (20,21) and hence adhesiveness (8), will alter the numerical interpretation of adhesiveness. Consequently, it is important to quote probe speed when describing these mechanical parameters.

Formulations rheology was significantly affected by the concentration of each polymeric component. Consequently, increased concentrations of HEC, PVP and PC significantly increased the viscosity of the formulations. These increased viscosities showed good correlation with increased product hardness and compressibility, reflecting the importance of viscosity on these compression characteristics. The general rheograms of each formulation were pseudoplastic with thixotropy. Therefore, following application of shearing stresses of increasing magnitudes, there was a general loss of consistency of each formulation, i.e. shear thinning. This property would be expected to be advantageous whenever the formulations are applied to the oral mucosae.

In conclusion, this study has shown that TPA may be conveniently and rapidly employed to mechanically and physically characterise bioadhesive formulations which have been designed for topical application to the oral cavity. The mechanical parameters described by TPA that are directly applicable to the development of such products are hardness, compressibility, adhesiveness and cohesiveness. The choice of candidate formulations for clinical examination will require a compromise between low hardness and compressibility (to ensure ease of product removal from the container and ease of application onto the oral mucosae), maximal adhesiveness (to ensure good retention within the mouth) and high cohesiveness (to ensure complete structural recovery following application). Consequently, it is suggested that the adhesiveness, compressibility, cohesiveness and hardness values exhibited by formulations containing 3% HEC, 3% PVP and 0.5 or 1% PC would be the most appropriate for clinical examination. Product hardness, compressibility and adhesiveness were directly influenced by viscosity, highlighting the importance of product rheology on these characteristics. In light of the findings of this study and, given the good correlation between mechanical characterisation of products using TPA and sensory evaluations of these parameters *in vivo* (22,23), TPA may be considered to be a useful analytical technique in the development of topical pharmaceutical formulations.

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