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Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers

David S. Jones *, A. David Woolfson, Andrew F. Brown

The Pharmaceutical Devices Group, School of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97, Lisburn Road, Belfast BT9 7BL, United Kingdom

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Abstract

This study examined the mechanical/textural, viscoelastic and mucoadhesive properties of a range of aqueous gels composed of either hydroxyethylcellulose (HEC) or sodium carboxymethylcellulose (Na CMC). The mechanical/textural properties of each formulation were determined using texture profile analysis. The viscoelastic properties of each formulation were examined over a defined frequency range (0.01–1.0 Hz) using oscillatory rheometry in conjunction with stainless steel parallel plate geometry. The mucoadhesive properties of the gels were evaluated by measuring the tensile force required to overcome the gel/mucin adhesive interaction. Both gel hardness and compressibility, properties that affect the ease of product removal from a container and spreadability, increased as a function of increasing polymer concentrations. This is attributed to the effects of HEC and Na CMC on gel viscosity. Gel adhesiveness, a property related to bioadhesion, also increased as a function of polymer concentration and is attributed to the reported adhesive nature of these polymers. Increasing frequency of oscillation increased the storage and loss moduli yet decreased both the dynamic viscosity of each gel type and also the loss tangent of HEC (but not Na CMC) gels. Therefore, following exposure to the range of oscillatory stresses that may be expected in vivo, HEC gels will be more susceptible than Na CMC gels to alterations in these rheological properties. Consequently, it would be expected that the clinical performance of HEC gels will be modified to a greater extent than Na CMC gels. In general, HEC gels exhibited a greater elastic nature than Na CMC gels over the frequency range employed for oscillation. The storage and loss moduli and dynamic viscosity of both gel types increased, yet the loss tangent of both gel types decreased as a function of increasing polymer concentration. Gel mucoadhesive strength was dependent on both the time of contact of the formulation with mucin and also on polymer concentration. In conclusion, this study has characterised a number of gels containing either HEC or Na CMC in terms of their mechanical/textural, viscoelastic and mucoadhesive properties. Due to its relevance to the clinical performance, it is suggested that the information derived from these methods may be usefully combined to provide a more rational basis for the selection of polymers and their formulation as topical drug delivery systems. © 1997 Elsevier Science B.V.

Keywords: Texture profile analysis; Viscoelasticity; Cellulose polymers; Mucoadhesion; Hardness; Compressibility; Adhesiveness

* Corresponding author.

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1. Introduction

Polymers that can form adhesive interactions with biological substrates have been reported by several authors to offer certain advantages for drug delivery, including, prolonged residence time and improved location on, e.g. the gastrointestinal tract, buccal cavity, nasal and vaginal tracts, the eye and the cervix (Nagai et al., 1984; Ch'ng et al., 1985; Bouckaert et al., 1992; Woolfson et al., 1995a; Jones et al., 1996a). Cellulose polymers, e.g. hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, are examples of polymers that have been reported to possess adhesive properties. Chemically, these linear polymers are cellulose derivatives possessing various degrees of substitution that may be ionic or non-ionic (Bird et al., 1987; Lin et al., 1993). Consequently, following addition to an aqueous phase, these cellulose derivatives undergo swelling prior to dissolution. Pharmaceutically, water soluble cellulose polymers have found widespread applications, e.g. in the formulation of solid dosage forms, aqueous disperse systems as viscosity enhancing agents and in products for topical application (Peppas, 1987).

In the development of topical dosage forms, several desirable attributes that contribute to the ultimate patient acceptability and clinical efficacy of the product may be defined. These include optimal mechanical properties (e.g. ease of removal of product from the container, good spreadability on the substrate, e.g. skin, mucous membranes), good bioadhesion (to ensure retention at the site of application), acceptable viscosity, drug release and drug absorption (Davis, 1971; Schwartz, 1975; Jones et al., 1996a). However, products designed for topical administration will be subjected to shearing forces, e.g. chewing, breathing, swallowing, talking, flexing processes of skin, that are oscillatory in nature. Therefore, it is important to examine the effects of such oscillatory forces on the product rheology, and hence, on their clinical performance.

To date, there have been few studies that have described both the mechanical, rheological (oscillatory) and also mucoadhesive properties of topical pharmaceutical gels. Recently, we described a rapid, straightforward analytical technique, texture profile analysis (TPA), that may be applied to the mechanical characterisation of pharmaceutical gels and semi-solid systems (Jones et al., 1996a,b). In this, a solid analytical probe is twice depressed into a sample to a defined depth and at a defined rate, allowing a delay period between successive compressions. From the resultant force-time plot, the following mechanical parameters may be described:

1. hardness (force required to attain a given deformation)
2. adhesiveness (the work necessary to overcome the attractive forces between the surface of the sample and the surface of the probe)
3. compressibility (the work required to deform the product during the first compression of the probe)

These mechanical properties have been directly correlated with sensory parameters in vivo, e.g. removal of the product from the container, application characteristics of the product, and are therefore directly applicable to the design of topical pharmaceutical preparations (Schwartz, 1975; Jones et al., 1996b)

The present study characterises the mechanical, rheological and mucoadhesive properties of aqueous gels prepared from a non-ionic (hydroxyethylcellulose) and ionic (sodium carboxymethylcellulose) cellulose polymer that are commonly employed for the formulation of topical formulations. TPA and oscillatory rheometry are used to quantify the mechanical and textural properties of the gels, and the effect of oscillatory stresses similar to those experienced under physiological conditions, on their structural properties. In addition, the adhesive properties of the gels to both mucin and inert substrates are presented. This study therefore a complete characterisation and evaluation of cellulose polymers as platforms for oral, topical drug delivery systems.

2. Materials and methods

2.1. Chemicals

Hydroxyethylcellulose (Natrosol 250 HHX-Pharm) and sodium carboxymethylcellulose (Blanose 7HF) were gifts from Aqualon (Warrington, UK). Crude pig gastric mucin was purchased from Sigma (St. Louis, MO). All other chemicals were purchased from BDH (Poole, England) and were of AnalaR, or equivalent, quality.

2.2. Manufacture of pharmaceutical gels

Gels containing the appropriate concentrations of hydroxyethylcellulose (HEC), or sodium carboxymethylcellulose (Na CMC) were prepared by dissolving the required mass in the phosphate buffered saline (PBS, pH 6.8, 0.01 M) with vigorous stirring using a mechanical stirrer (Heidolph). Following manufacture, all gels were placed in a vacuum to remove entrapped air, prior to storage at 4°C until required.

2.3. Texture profile analysis of pharmaceutical gels

Texture profile analysis (TPA) of pharmaceutical gels was performed using a Stable Micro Systems texture analyser (Model TA-XT 2) in texture profile analysis mode, as previously described (Jones et al., 1996a,b). Gels were packed to a fixed height in McCartney bottles, avoiding the introduction of air bubbles. The analytical probe (10 mm diameter) was then twice compressed into each sample at a defined rate (6 mm s^{-1}) and to a defined depth (15 mm), allowing a delay period of 15 s between consecutive compressions. All analyses were performed at least in quadruplicate on samples at ambient temperature.

2.4. Oscillatory rheometry of pharmaceutical gels

Oscillatory measurements were performed using a Carri-Med CSL^2-100 rheometer with a stainless steel parallel plate geometry (4 cm diameter) at 20 ± 0.1°C. The linear viscoelastic region of the formulations, identified as the region where stress was directly proportional to strain and G′ remained constant, was determined by torque sweep from 0.1 to 100 Pa at frequencies of 0.01 and 1.0 Hz. Oscillatory measurements were performed over a frequency range of 0.01–1.0 Hz employing a constant displacement of 3.25×10^{-4} rad for the frequency sweep analysis. Calculation of the storage modulus (G′), loss modulus (G″), loss tangent (tan δ) and dynamic viscosity (η') were performed using a computer programme supplied by TA Instruments (Leatherhead, UK).

2.5. In vitro mucoadhesion method

The mucoadhesive properties of HEC and Na CMC were evaluated using a TA-XT2 Texture Analyser (Stable Micro Systems). Mucin discs were manufactured by compression of mucin (250 mg) using a ring press with a 13 mm die and a compression force of 10 tonnes, applied for 30 s. These were then horizontally attached to the lower end of the TPA probe using double sided adhesive tape. Samples of pharmaceutical gels were packed into shallow cylindrical vessels and the analytical probe containing the mucin disc was lowered onto the surface of each formulation and a downward force of 0.1 N applied for a predefined time (0.5, 2, 4, 6, 8, 10 min) to ensure intimate contact between the mucin disc and the sample. The probe was then moved vertically upwards at a constant speed of 1.0 mm s^{-1} and the force required to detach the mucin disc from the surface of each formulation was determined from the resultant force-time plot. All measurements were performed, at least, in quadruplicate.

2.6. Statistical analysis

The effects of concentration on textural parameters, namely, the hardness, compressibility add adhesiveness of gels composed of HEC or Na CMC were statistically evaluated using a one-way analysis of variance (ANOVA). Similarly the effects of polymer concentration on the viscoelastic properties of each gel (storage modulus, loss modulus, loss tangent and dynamic viscosity) at representative (0.062, 0.1142, 0.5307, 0.9478 Hz) were evaluated using a one-way ANOVA. Finally, the effects of polymer concen-

Table 1
The mechanical properties of hydroxyethylcellulose (HEC) gels (hardness, compressibility, adhesiveness), as determined using texture profile analysis

Concentration of HEC (% w/w)	Hardness[a] (N)	Adhesiveness[a] (N mm)	Compressibility[a] (N mm)
3	0.34 ± 0.01	3.03 ± 0.20	3.08 ± 0.07
4	0.88 ± 0.06	6.44 ± 0.06	8.03 ± 0.59
5	1.46 ± 0.06	14.22 ± 0.03	13.48 ± 0.84
6	2.36 ± 0.02	19.89 ± 1.05	21.44 ± 0.65
8	3.56 ± 0.11	30.14 ± 3.15	33.27 ± 0.44
10	5.13 ± 0.12	42.06 ± 1.60	50.47 ± 0.40
12	7.20 ± 0.15	46.36 ± 4.68	70.12 ± 1.94

[a] Mean ($\pm$ S.D.) of at least four replicate measurements.

tration and duration of contact with mucin on the force required for detachment of the mucin-formulation adhesive interaction were statistically evaluated using a two-way ANOVA. Post-hoc comparisons of the means of individual groups were performed using Scheffe's test. For all analyses, $p < 0.05$ denoted significance.

3. Results

The mechanical properties of aqueous pharmaceutical gels composed of HEC or Na CMC are presented in Tables 1 and 2, respectively. For both polymeric systems, each incremental increase in polymeric concentration significantly altered their mechanical properties, resulting in increased gel hardness, increased work required to compress each gel to a fixed distance (compressibility) and increased adhesiveness of the gel to the analytical probe. Interestingly, increasing the concentrations of HEC from 10 to 12% w/w, or alternatively, Na CMC from 18 to 20% w/w did not alter product adhesiveness.

Figs. 1–4 illustrate the viscoelastic properties of aqueous gels composed of a range of concentrations of HEC (3–12% w/w). For all formulations, the storage modulus increased as a function of increasing oscillatory frequency (Fig. 1), whereas the loss tangent (the ratio of G″ to G′, Fig. 3) and the dynamic viscosity (Fig. 4) both decreased. Typically, the dynamic viscosity of HEC gels was high at low frequencies and decreased monotonically as the frequency was increased. In general, the loss modulus of HEC gels was independent of oscillatory frequency at frequencies exceeding 0.1 Hz (Fig. 2). Selecting four frequencies (0.062, 0.1142, 0.5307, 0.9478 Hz) to represent the range of frequency sweep analysis, the effects of concentration of HEC on the viscoelastic properties were statistically examined. Increasing the concentration of HEC in aqueous gels significantly increased their storage modulus, loss modulus and dynamic viscosity yet decreased the loss tangent ($\tan \delta$) at each representative frequency.

Figs. 5–8 present the effects of concentration of Na CMC in aqueous gels and oscillatory frequency on the storage modulus (Fig. 5), loss modulus (Fig. 6), loss tangent (Fig. 7) and dynamic viscosity (Fig. 8). In a similar fashion to HEC gels, increasing oscillatory frequencies significantly increased the storage modulus, loss modulus and decreased the dynamic viscosity. In addition, Na CMC gels displayed large values of η' at low frequencies that decreased monotonically as the oscillatory frequency was increased. Oscillatory frequency did not affect the loss tangent ($\tan \delta$). Once more, the effects of concentration of Na CMC on G′, G″, η' and $\tan \delta$ were statistically evaluated at frequencies representative of frequency sweep analysis, as described earlier. Increased concentrations of Na CMC (6–20% w/w) significantly increased their storage modulus, loss modulus, dynamic viscosity but had no significant effect on the loss tangent ($\tan \delta$).

The effects of formulation contact time with mucin and of concentration on the force required to overcome the gel/mucin adhesive

Table 2
The mechanical properties of sodium carboxymethylcellulose (Na CMC) gels (hardness, compressibility, adhesiveness), as determined using texture profile analysis

Concentration of Na CMC (% w/w)	Hardness (N)[a]	Adhesiveness[a] (N mm)	Compressibility[a] (N mm)
6	0.24 ± 0.05	1.09 ± 0.16	1.87 ± 0.34
9	0.98 ± 0.04	7.46 ± 0.41	7.46 ± 0.07
12	2.67 ± 0.04	20.06 ± 2.07	23.68 ± 1.50
15	4.46 ± 0.20	30.29 ± 1.56	40.72 ± 2.31
18	6.61 ± 0.37	40.64 ± 3.57	58.70 ± 4.63
20	8.64 ± 0.28	45.30 ± 2.82	78.13 ± 3.41

[a] Mean (± S.D.) of at least four replicate measurements.

bonds are presented in Tables 3 and 4 for HEC and Na CMC, respectively. In general, for both polymeric systems, increasing the time of contact of formulation with mucin prior to evaluation of the mucoadhesive bond strength significantly increased the strength of interaction between formulation and mucin. In addition, by increasing the concentration of polymer in the formulations, the strength of mucoadhesive bond increased. However, a plateau in mucoadhesive strength was observed for HEC (circa 8% w/w) and Na CMC (18% w/w), beyond which no obvious gain in formulation mucoadhesive strength could be achieved. At this plateau region, the mucoadhesive strength of gels containing Na CMC was significantly greater than for those containing HEC. Gels containing concentrations of HEC that were less than 5% w/w or containing concentrations of Na CMC that were less than 12% w/w exhibited cohesive (gel–gel) bond failure in tensile testing and, therefore, the strength of the adhesive interaction between formulation and mucin could not be determined.

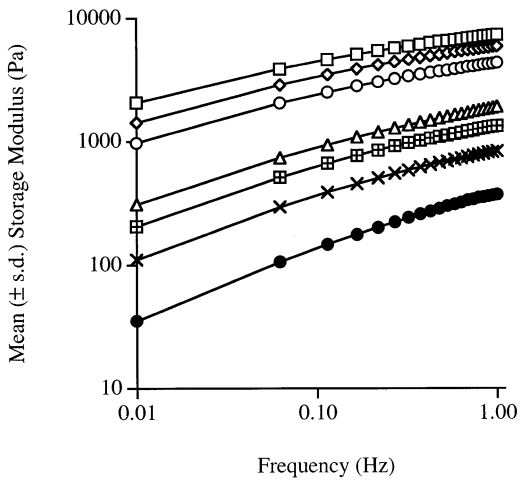

Fig. 1. The effects of polymer concentration (% w/w) and oscillatory frequency on the storage modulus (G′) of gels composed of hydroxyethylcellulose. Key: 3% w/w (●), 4% w/w (☆), 5% w/w (☒), 6% w/w (△), 8% w/w (○), 10% w/w (◇) and 12% w/w (□). Each datum represents the mean (± S.D.) of at least three replicate measurements.

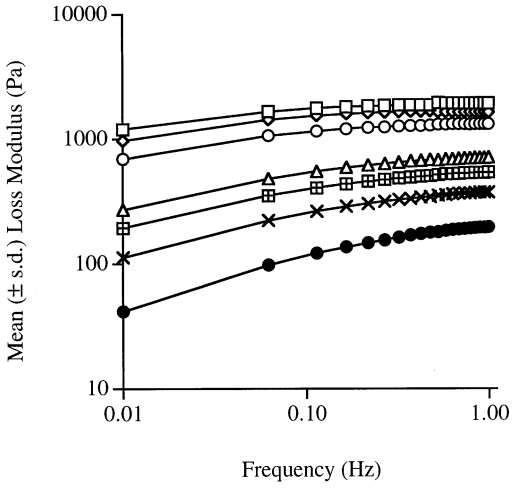

Fig. 2. The effects of polymer concentration (% w/w) and oscillatory frequency on the loss modulus (G″) of gels composed of hydroxyethylcellulose. Key: 3% w/w (●), 4% w/w (☆), 5% w/w (☒), 6% w/w (△), 8% w/w (○), 10% w/w (◇) and 12% w/w (□). Each datum point represents the mean (± S.D.) of at least three replicate measurements.

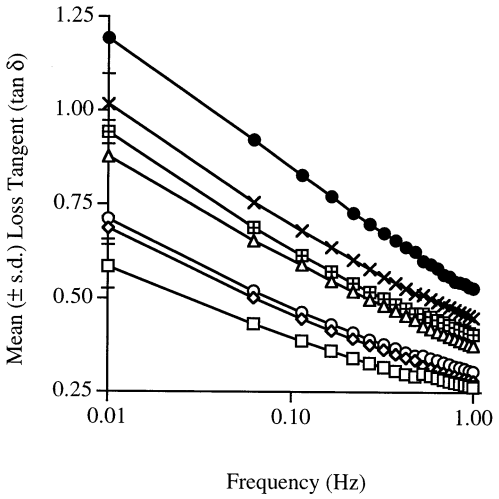

Fig. 3. The effects of polymer concentration (% w/w) and oscillatory frequency on the loss tangent (tan δ) of gels composed of hydroxyethylcellulose. Key: 3% w/w (●), 4% w/w (☆), 5% w/w (☒), 6% w/w (△), 8% w/w (○), 10% w/w (◇) and 12% w/w (□). Each datum point represents the mean ($\pm$ S.D.) of at least three replicate measurements.

4. Discussion

The physical characterisation of pharmaceutical gels and semi-solids has been described in several studies using a variety of analytical techniques. These include creep analysis (Barry and Meyer, 1979a), flow rheometry (Barry and Meyer, 1979a; Pena et al., 1994), oscillatory rheometry (Barry and Meyer, 1979b; Craig et al., 1994; Tamburic and Craig, 1995), dielectric spectroscopy (Craig et al., 1994; Tamburic and Craig, 1995), FTIR (McTaggart and Halbert, 1994) and gel strength/shear and compression analysis (Ferrari et al., 1994; Lucero et al., 1994a). These studies provide information concerning the structural and rheological properties of gels and semi-solids that may be related to product performance, e.g. drug release (Talukdar et al., 1996) and product stability (Davis, 1971). However, such techniques can not directly evaluate the textural properties of formulations, e.g. ease of removal from the container, ease of application to the skin, retention of the product at the site of application and the after feel of the product, properties that must be considered in the design of topical products. Therefore, this study represents one of the first to employ both non-destructive rheology, to convey information concerning both the physical structure of the gels and to predict the effects of stresses encountered under physiological conditions on their structural properties, and also texture profile analysis (TPA) to characterise the mechanical and textural properties of gel systems. The information derived from TPA has been shown to correlate with textural properties in vivo (Szczesniak et al., 1963; Schwartz, 1975) and therefore this method is useful in the selection of potential candidates for topical use. In addition, in the development of topical mucosal adhesive dosage forms, it is useful to quantify the interaction between the dosage form and mucosal substrate. However, there are few methods available that may be employed to quantify the strength of interaction of gel systems with either mucous epithelia or mucin. The majority of methods have employed tensile analysis (e.g. Caramella et al., 1994; Dyvik and Graffner, 1992). However, as the strength of the cohesive bonds associated with pharmaceutical gels is frequently lower than the gel-mucin adhesive bonds, direct quantification of gel mucoadhesion may not

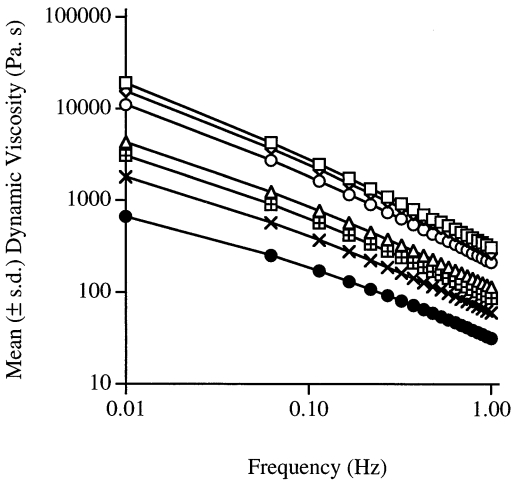

Fig. 4. The effects of polymer concentration (% w/w) and oscillatory frequency on the dynamic viscosity (η') of gels composed of hydroxyethylcellulose. Key: 3% w/w (●), 4% w/w (☆), 5% w/w (☒), 6% w/w (△), 8% w/w (○), 10% w/w (◇) and 12% w/w (□). Each datum represents the mean ($\pm$ S.D.) of at least three replicate measurements.

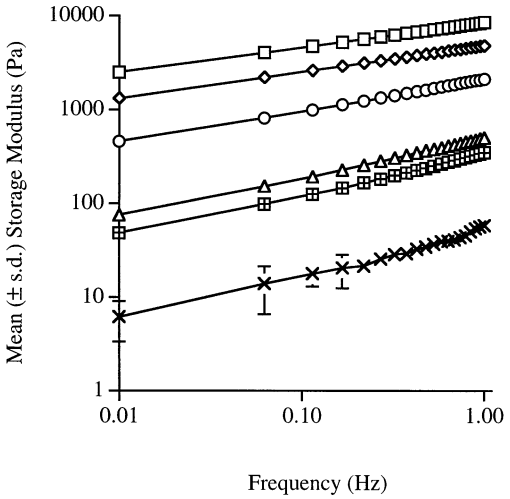

Fig. 5. The effects of polymer concentration (% w/w) and oscillatory frequency on the storage modulus (G′) of gels composed of sodium carboxymethylcellulose. Key: 6% w/w (●), 9% w/w (☆), 12% w/w (☒), 15% w/w (○), 18% w/w (◇) and 20% w/w (□). Each datum point represents the mean (± S.D.) of at least three replicate measurements.

be performed. In this current study, this problem was primarily overcome by the use of a compressed mucin disc in conjunction with tensile analysis.

Three main textural properties of the cellulose gels under investigation were described in this study, namely, hardness, compressibility and adhesiveness. There have been few studies that have described gel hardness. However, Ferrari et al. (1994) described increased hardness (strength) of aqueous hydroxypropylmethylcellulose gels as a function of polymeric concentration. Similarly, this study has described increased gel hardness as a function of the concentration of cellulose polymers. Compressibility describes the work required to compress the product through a fixed distance. Given the nature of the analysis, this parameter also describes the work required to enable spreading of the product over the surface of the probe. Other studies have examined the spreadability of pharmaceutical gels. However, these methods are often time consuming, involving time dependent measurements of the diameter of product spreading following application of a known weight(s) (e.g. Vennat et al., 1994; Lucero et al., 1994b). The compressibility of HEC and Na CMC gels increased as a function of the concentration of each of the polymeric components. In addition, good correlation was observed between gel hardness and compressibility. Product hardness and compressibility are rheological parameters that quantify product deformation under both compression and shear. Therefore, the effects of these polymers on these parameters may be explained by their concentration-dependent effects on product viscosity. Similarly, Lucero et al. (1994a) described a correlation between the apparent viscosity of formulations and their spreadability.

All formulations examined in this study exhibited wide ranges of viscoelastic properties that were dependent both on the concentration of the constituent polymers, i.e. HEC and Na CMC, and also on the oscillatory frequency. In all cases, the storage modulus increased as the frequency of oscillation increased, indicating a greater elastic character. This is consistent with the Maxwellian description of the response of viscoelastic materials to oscillatory stresses (Barry, 1974). Thus, at high frequencies, sufficient time is available to

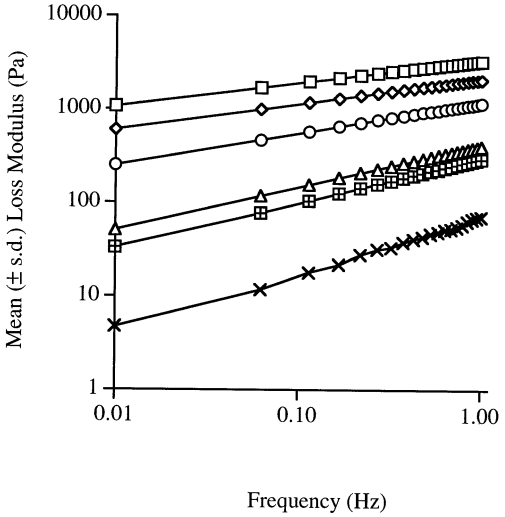

Fig. 6. The effects of polymer concentration (% w/w) and oscillatory frequency on the loss modulus (G″) of gels composed of sodium carboxymethylcellulose. Key: 6% w/w (☆), 9% w/w (☒), 12% w/w (△), 15% w/w (○), 18% w/w (◇) and 20% w/w (□). Each datum represents the mean (± S.D.) of at least three replicate measurements.

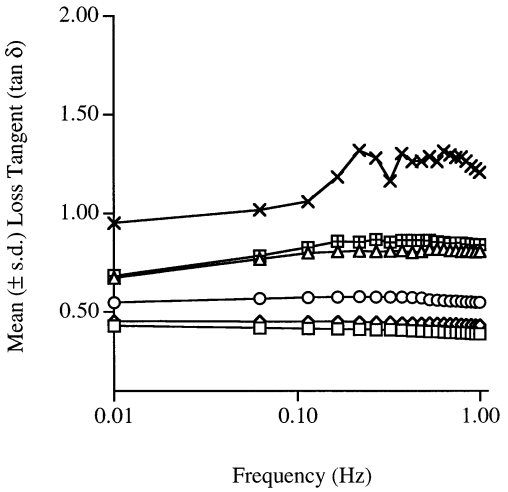

Fig. 7. The effects of polymer concentration (% w/w) and oscillatory frequency on the loss tangent (tan δ) of gels composed of sodium carboxymethylcellulose. Key: 6% w/w (☆), 9% w/w (☒), 12% w/w (△), 15% w/w (○), 18% w/w (◇) and 20% w/w (□). Each datum point represents the mean (± S.D.) of at least three replicate measurements.

enable spring elongation and contraction under the imposed oscillatory shear, however, there is insufficient time available to allow for dashpot movement. Consequently, at these frequencies, the gels behaved as an elastic solid. As the oscillatory frequency is decreased, there is more time available to allow for dashpot extension and thus the materials exhibit properties characteristic of both solids and liquids. Ultimately, the storage modulus of all materials should approach zero, however, this was not observed in any of the gel systems.

With the exception of some of the more dilute polymeric gels, e.g. those containing 3% w/w HEC or 6% w/w Na CMC, all formulations exhibited predominantly elastic behaviour, evident from the greater magnitude of the storage modulus (G′) to that of the loss modulus (G″). The loss tangent is commonly employed to characterise the relationship between these two parameters and is described as the ratio of the energy lost (G″) to energy stored (G′) in an oscillatory cycle (Barry and Meyer, 1979b). Interestingly, gels composed of HEC displayed decreased tan δ values associated with increasing frequency, whereas the loss tangent remained constant over the frequency range examined for Na CMC gels. Therefore, the viscoelastic properties of HEC gels were more frequency dependent than those of Na CMC gels. Both polymeric systems exhibited a concentration-dependent decrease in tan δ, thus confirming the increased elastic nature of these formulations.

The observed large dynamic viscosities (η') of gels at low oscillatory frequencies that decreased at higher frequencies is also characteristic of viscoelastic systems (Davis, 1971; Barry and Meyer, 1979b). Extrapolation of the plots of log η' vs. log frequency to 0 Hz allows an estimation of the steady state viscosity (Davis, 1971), from which it was determined that greater concentrations of either HEC or Na CMC increased the steady state viscosity of the resultant gels (results not shown). In addition, the steady state viscosities of each gel showed good correlation with both product hardness and compressibility, confirming the role of viscosity in these two textural parameters.

A product designed for topical application to a biological substrate, e.g. mucous membranes or skin, should preferably possess adhesive properties, as these will enhance the time of location at

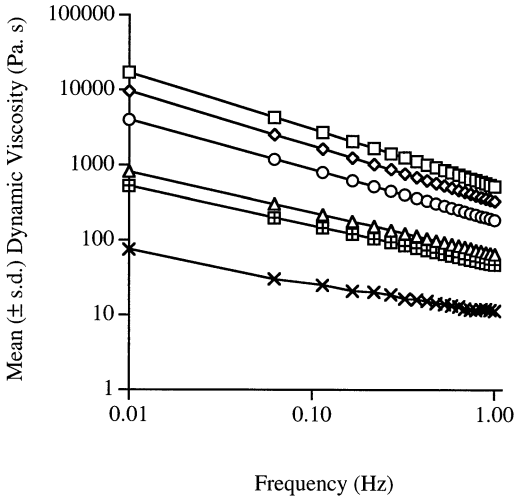

Fig. 8. The effects of polymer concentration (% w/w) and oscillatory frequency on the dynamic viscosity (η') of gels composed of sodium carboxymethylcellulose. Key: 6% w/w (☆), 9% w/w (☒), 12% w/w (△), 15% w/w (○), 18% w/w (◆) and 20% w/w (□). Each datum represents the mean (± S.D.) of at least three replicate measurements.

Table 3
The effects of polymer concentration and duration of contact with mucin on the mucoadhesive properties of hydroxyethylcellulose (HEC) gels

Duration of contact (min)	Mean (±S.D.) force required to break the adhesive bond between mucin and gels composed of HEC				
	HEC 5% w/w	HEC 6% w/w	HEC 8% w/w	HEC 10% w/w	HEC 12% w/w
0.5	Cohesive failure	0.22 ± 0.02	0.23 ± 0.03	0.20 ± 0.02	0.23 ± 0.02
2	0.34 ± 0.03	0.35 ± 0.18	0.44 ± 0.03	0.36 ± 0.03	0.38 ± 0.04
4	0.39 ± 0.02	0.49 ± 0.01	0.63 ± 0.03	0.50 ± 0.02	0.60 ± 0.04
6	0.43 ± 0.01	0.55 ± 0.02	0.63 ± 0.03	0.63 ± 0.01	0.66 ± 0.02
8	0.50 ± 0.02	0.54 ± 0.02	0.66 ± 0.02	0.66 ± 0.01	0.65 ± 0.02
10	0.54 ± 0.02	0.60 ± 0.01	0.68 ± 0.04	0.77 ± 0.04	Not determined

the site of application and hence improved clinical efficacy (Woolfson et al., 1992). The two polymers selected for examination in this study have been described as bioadhesive (Smart et al., 1984) and, consequently, exhibited concentration-dependent adhesive interactions with both mucin and also with the polymeric probe in TPA (termed adhesiveness). Whilst the two methods quantify the extent of adhesion, the type of adhesive bond formed on the two different substrates and also the factors affecting these adhesive bonds differ. Adhesiveness in TPA is commonly defined as the work required to overcome the attractive forces between the surface of the sample and the surface of the probe (Jones et al., 1996a). However, adhesiveness is a measure of the work required to remove the probe from the sample, which may in some cases involve fracture of cohesive bonds within the sample, and therefore is partly dependent on sample tack. The effects of polymer concentration on gel adhesiveness is therefore due to both increased interactions between polymeric molecules and the analytical probe and also due to increased product tack. Interestingly, no further increases in adhesiveness were observed above a certain concentration which varied with polymer type. This may be due to high cohesive bond strength in these samples that prevents the formation of adhesive interactions with the probe. It is therefore suggested that product adhesiveness is, more appropriately, a reliable comparative measure of adhesive affinity of candidate formulations for non-mucous surfaces, e.g. skin.

The mucoadhesive properties of the polymeric gels were dependent both on the initial time of contact between mucin and each formulation, and also on the concentration of each polymeric component. In addition, it is accepted that Na CMC exhibits greater mucoadhesive properties than HEC (Smart et al., 1984), a property that was observed in this study. The former contact time-dependency of mucoadhesion conforms to the interpenetrating theory of mucoadhesion, proposed by Smart et al. (1984) and Ponchel et al. (1993). Therefore, the provision of greater contact times between the two interfaces allowed for the movement of water from the gels to the solid mucin disc, which thus ensured swelling of mucin and enabled interpenetration of the mucin polymeric chains with HEC or Na CMC in the gel systems. Increasing concentrations of HEC or Na CMC increased the strength of the mucoadhesive bond up to a maximum concentration. Beyond this concentration the amount of free water in the gels was decreased and therefore the amount of water available to produce swelling of mucin decreased, thus reducing the strength of mucin/gel adhesive bond. Similarly, increased time of contact between mucin and the formulations allowed greater time for swelling of mucin and hence increased the interaction between the polymeric chains of each interface. Once more, a maximum time of contact between the two phases was evident and was a result of no transfer of water from the gel to mucin. Decreased bioadhesive strengths of bioadhesive systems has been

Table 4
The effects of polymer concentration and duration of contact with mucin on the mucoadhesive properties of sodium carboxymethylcellulose (Na CMC) gels

Duration of contact (min)	Mean (S.D.) force required to break the adhesive bond between mucin and gels composed of Na CMC		
	Na CMC 15% w/w	Na CMC 18% w/w	Na CMC 20% w/w
0.5	0.37 ± 0.02	0.45 ± 0.03	0.61 ± 0.04
2	0.47 ± 0.02	0.62 ± 0.00	0.64 ± 0.03
4	0.52 ± 0.01	0.80 ± 0.02	0.80 ± 0.05
6	0.53 ± 0.02	0.86 ± 0.09	0.81 ± 0.04
8	0.61 ± 0.04	0.97 ± 0.02	1.13 ± 0.09
10	0.63 ± 0.01	1.05 ± 0.09	1.02 ± 0.08

reported to be due to overhydration of the interface between the two adherent phases (e.g. Woolfson et al., 1995b) However, this was not observed for the formulations examined in this mucoadhesion assay.

The information obtained from the various analytical methods may be employed in both the selection of candidate formulations for as platforms for topical administration, and also to predict the effects of physiological stresses on product performance. Optimally, topical preparations should exhibit a number of advantageous characteristics, including ease of removal from the container, good spreadability on and adherence to the substrate and tolerance to the effects of physiological stresses on product rheology. It is apparent from the results of this study that a compromise must be attained between high product adhesiveness/mucoadhesion and product hardness and compressibility, as, in general, these parameters were increased as a function of polymer concentration. Products possessing high hardness and compressibility properties will be difficult to remove from the container and apply to the substrate and, as a result, may be perceived as unacceptable by the end user (Schwartz, 1975). In addition, products designed for application to the oral cavity that exhibit high hardness will be perceived as uncomfortable, given the good correlation between in vitro and in vivo measurements of this parameter (Szczesniak et al., 1963). For this reason, formulations containing higher concentrations of either HEC and Na CMC are deemed unacceptable for clinical use. It is also suggested that consideration of the effects of oscillatory stresses on product performance should be performed in the design of topical formulations. Ideally, products should be formulated so that their structural rheology is relatively independent of oscillatory frequency. In general, this property was demonstrated by gels containing Na CMC as was evident from the frequency-independent loss tangent response of these systems. However, at higher oscillatory frequencies (e.g. those experienced by chewing, talking), HEC gels adopted greater elastic character. Therefore, under these conditions, product performance in respect of bioadhesion (Tamburic and Craig, 1995) and drug release will differ from that observed at lower oscillating frequencies. It would be expected that gels containing Na CMC would display a relatively constant clinical performance over a range of oscillatory frequencies.

In conclusion, this study has characterised a number of gels containing either HEC or Na CMC in terms of mechanical and textural, rheological and mucoadhesive properties. Such information can provide a more rational basis for the selection of polymers and their formulation as topical drug delivery systems.

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