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Research paper

A comparison of different in vitro methods for measuring mucoadhesive performance

Slobodanka Tamburic, Duncan Q.M. Craig *

Centre for Materials Science, University of London, London, UK

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Abstract

The purpose of this study was to assess and compare several in vitro methods for measuring mucoadhesive performance, using a controlled-stress rheometer and a penetrometer (texture analyser). Three poly(acrylic acid) (PAA) polymers, differing in their cross-linking status, were selected, namely Carbopol 974P, Carbopol 971P and Noveon AA-1 (polycarbophil). The polymers were used in two neutralisation states (acidic and neutralised with triethanolamine) and two physical states (hydrogel and compact). The in vitro methods tested were categorised as 'bulk' and 'tensile'. Bulk techniques concerned the structure analysis of polymer gels and polymer/mucin mixtures by oscillatory rheology and penetrometry. Rheological synergy, dependent on the frequency of oscillation, was detected in the case of neutralised PAA/mucin mixtures, as opposed to unneutralised mixtures, where only a decrease in elasticity were found. A linear relationship was found between the phase angle δ and the area under the penetration/withdrawal curve when samples of similar structure were examined. The tensile methods involved the assessment of maximum detachment force and work of adhesion between polymer gels (or compacts) and a layer of 30% mucin gel. In the case of compacts, the hydration time was varied from 1 to 20 min and was found to affect the mucoadhesive performance. The tensile methods detected differences in mucoadhesive properties among the three structurally similar polymers, giving the same rank order as was found for the rheological properties. © 1997 Elsevier Science B.V.

Keywords: Carbomer; Mucoadhesion; Oscillatory rheology; Polycarbophil; Tensile test; Texture analysis

1. Introduction

The scope and aims of bio- and mucoadhesive research have broadened over recent years to include not only the search for good adhesive candidates but also the evaluation of physiological features of mucoadhesive polymers, such as the inhibition of proteolytic enzymes and increase in epithelial permeability [1,2]. While in the field of local drug delivery (nasal, intraoral, ocular, vaginal and rectal) mucoadhesive polymers have proven to be highly useful [3], oral delivery has been less successful, largely due to the limits associated with the physiology of the gastrointestinal tract. Furthermore, the nature of the interaction between the drug delivery systems and the mucus layer is still not fully understood. Mucoadhesion is known to be a very complex phenomenon, depending on the properties of polymer, biological tissue and the surrounding environment. It is recognised that every theoretical development has distinct limitations and that the operative mechanism probably involves a combination of several of these processes [4], the most commonly quoted explanations involving surface energy thermodynamics and interpenetration theories [5].

* Corresponding author. Centre for Materials Science, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK; Tel.: +44 171 7535863; fax: +44 171 7535920; e-mail: duncraig@cua.ulsop.ac.uk

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One approach to the study of mucoadhesion is rheological characterisation of mucoadhesive interface. It is based on the assumption that the extent of interpenetration can be detected by measuring differences in rheological parameters between polymer gels and their mixtures with mucin. The synergistic increase in viscosity was proposed as an index of bioadhesion bond strength by Hassan and Gallo [6]. This idea has later gained experimental support by a number of authors [7–11], using both flow and dynamic (oscillatory) techniques, although the results obtained may not always correspond to the bioadhesive behaviour [12].

The primary aim of this study was to further investigate the validity of the rheological approach by testing three structurally similar PAA polymers: Carbopol 974P (which is a benzene-free alternative to Carbopol 934P), Carbopol 971P (recently introduced as a less cross-linked variation of 974P) and Noveon AA-1 (known as polycarbophil). The rheological approach was compared with a tensile test, the latter being conducted using two experimental settings whereby the detachment parameters associated with both polymer gels and compacts from a mucin surface were analysed. These two systems were selected in order to test the mucoadhesive properties of polymers in different hydration states, since the hydration process may be highly relevant to mucoadhesion [13]. A further aim of the study was to assess the use of texture analysis in the field of structural evaluation of mucoadhesive gels and polymer/mucin mixtures by comparison with oscillatory rheology, which is a more established method of gel characterisation.

2. Materials and methods

2.1. Materials

Two carbomers, Carbopol 974P and Carbopol 971P and a polycarbophil, Noveon AA-1, were supplied by B.F. Goodrich (Cleveland, OH). The three materials possess similar chemical structure, being high-molecular weight, synthetic polymers of acrylic acid, but differing in their cross-linking status. Carbopols 974P and 971P have the same bifunctional cross-linker, with 971P being considerably less cross-linked [14]. Noveon AA-1 contains a tetrafunctional cross-linking agent, divinyl glycol [14]. All three polymers have been approved for use in oral and mucosal contact applications. An organic base, triethanolamine (TEA, Sigma, UK) was used for the neutralisation of the PAA hydrogels. A partially purified porcine gastric mucin (mucin type III, Sigma, UK) was used as a mucus substitute; this material was considered suitable in this case due to the comparative nature of the investigation and the quantity of material required for the studies.

2.2. Methods

2.2.1. Preparation of polymer gels and polymer/mucin mixtures

Unneutralised gels of 2.5% w/w Carbopol 974P, 971P and Noveon AA-1 were prepared by dispersing the polymer powder in de-ionised water by means of a paddle-stirrer mixer at 1200 rpm for 10 min. The gel samples were left to completely hydrate (2–3 h) and then were centrifuged at 3000 rpm for 30 min to remove air bubbles. The measurements were carried out 24 h after the centrifuging. Neutralised gel samples were prepared by adding polymer powder into the stirred mixture of triethanolamine and water. The weight ratio between PAA polymer and the base was 1:1.6 [15], with the final pH values of the hydrogels being in the range of 6.8–7.2.

In order to achieve an approximately isoviscous solution to the unneutralised PAA gels, a 10% w/w mucin gel in deionised water was prepared. Polymer/mucin

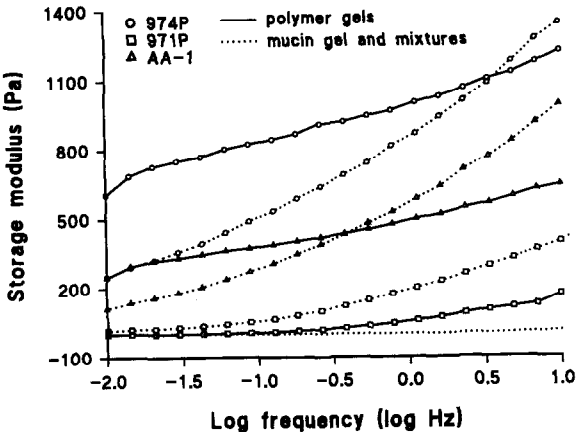

Fig. 1. Variation in the storage modulus with frequency for TEA neutralised polymer gels (solid lines with symbols), mucin gel (dotted lines) and polymer/mucin mixtures (dotted lines with symbols).

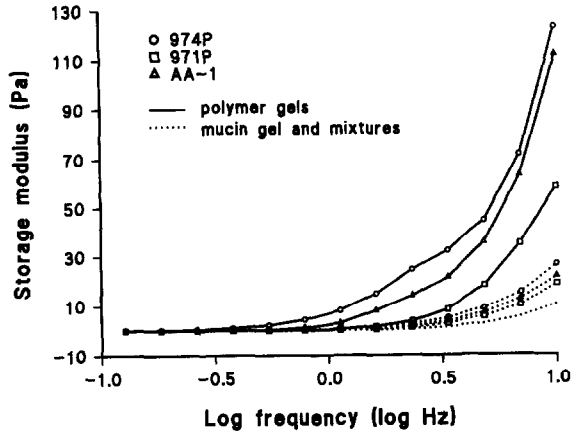

Fig. 2. Variation in the storage modulus with frequency for the unneutralised polymer gels (solid lines with symbols), mucin gel (dotted lines) and polymer/mucin mixtures (dotted lines with symbols).

Table 1
The percentage increase in storage modulus in the presence of mucin glycoproteins (G′ taken at 1.129 Hz)

Oscillatory data at 1.129 Hz			
Sample	G′ (Pa)polymer gel	G′ (Pa)polymer/mucin mixture	% Increase
Carbopol 974P+TEA	995.6 ± 13.4	806.4 ± 79.0	−19.0
Carbopol 974P	9.5 ± 0.9	0.6 ± <0.1	−93.6
Noveon AA-1+TEA	484.4 ± 20.4	603.3 ± 54.3	24.5
Noveon AA-1	3.7 ± 0.4	0.2 ± <0.1	−93.6
Carbopol 971P+TEA	61.7 ± 6.2	195.7 ± 4.8	217.1
Carbopol 971P	0.6 ± <0.1	0.4 ± <0.1	−32.8

Table 2
The percentage increase in storage modulus in the presence of mucin glycoproteins (G′ taken at 6.952 Hz)

Oscillatory data at 6.952 Hz			
Sample	G′ (Pa)polymer gel	G′ (Pa0 polymer gel	% Increase
Carbopol 974P+TEA	1177.0 ± 52.6	1290.0 ± 38.5	9.6
Carbopol 974P	71.8 ± 6.3	15.2 ± 1.3	−78.9
Noveon AA-1+TEA	624.0 ± 35.7	914.3 ± 70.2	46.5
Noveon AA-1	63.2 ± 6.0	10.1 ± 1.1	−83.9
Carbopol 971P+TEA	126.4 ± 10.7	363.9 ± 25.0	187.9
Carbopol 971P	35.1 ± 3.1	12.7 ± 1.2	−63.7

mixtures containing 10% w/w mucin and 2.5% w/w polymer were made by adding mucin powder into a stirred, freshly prepared PAA gel. The mixture was allowed to hydrate at the room temperature for 5–6 h, occasionally mixed with spatula, before being centrifuged at 3000 rpm for 30 min. All samples containing mucin were kept at 4°C when not used; they were evaluated within 48 h of preparation.

2.2.2. Preparation of polymer compacts

A quantity of 250 mg of polymer resin was compressed by a 1 t force for 60 s on an IR press. The compact diameter was 13 mm, providing a potential surface contact area of 1.33 cm^2. Given the possibility of different surface porosities of the top and bottom disc surfaces, the same (bottom) part was used in all mucoadhesive experiments.

2.2.3. Oscillatory rheology

The rheological properties of PAA gels and PAA/mucin mixes were evaluated using a Carri-med CSL 500 controlled-stress rheometer (TA Instruments, USA) with cone-and-plate test geometry. Oscillatory runs were carried out at 25°C, using a logarithmic frequency mode and a frequency range of 0.01–10 Hz under a 1350 μNm torque. The equilibrium time before every run was 5 min, and the sample volume approximately 0.8 ml. The tests were performed in triplicate, with a coefficient of variation of less than 10% found.

2.2.4. Texture analysis

A software-controlled penetrometer, TA-XT2 Texture Analyzer (Stable Micro Systems, UK), with a 5 kg load cell, a force measurement accuracy of 0.0025% and a distance resolution of 0.0025 mm was used in both texture analysis and tensile mucoadhesive experiments. Structural analysis were performed on PAA hydrogels (in both acidic and neutralised states), on 10% w/w mucin gel and on their mixtures by measuring the resistance to penetration and withdrawal of the probe. The pre-test speed was set up at 5 mm/s, the test speed at 1 mm/s and the penetration depth at 5 mm, with an acquisition rate of 100 points/s. The probe used was a plastic cylinder with a diameter of 13 mm. The study was carried out at room temperature (25°C) with at least five repeats obtained for each sample, with coefficients of variation less than 5% found.

2.2.5. Tensile tests

The mucoadhesive performance of the PAA hydrogels and compacts was measured by means of a Texture Analyzer, using two different procedures. In both cases, a cylindrical plastic probe (1.33 cm^2 surface area), covered with a thin layer of 30% mucin gel, was brought in contact with the sample, held for 60 s, and withdrawn at a speed of 0.1 mm/s.

When dealing with semisolid systems, a gel sample was placed in the metal cylinder and covered with a cap with central hole of 1.4 cm diameter. The surface of the exposed gel was carefully flattened and the cylinder

secured below the mucin-covered probe. The probe was then brought in contact with the PAA gel, lowered for further 0.2 mm and held for 60 s.

In the case of solid systems, the compact was fixed to the lower platform with a contact adhesive (Thixofix, Dunlop Adhesives, UK), after a double-sided adhesive tape failed to maintain good contact during tensile experiment. The compact was then wetted by 0.1 ml of deionised water (instilled by a syringe onto the centre of a compact and instantly spread over the whole surface) and left to hydrate for 1, 3, 5, 10 and 20 min, respectively, before testing. Upon making contact between a hydrated surface of a PAA compact and the layer of 30% mucin gel, a constant force of 0.5 N was imposed for 60 s. At least seven replicas were made for each sample.

3. Results and discussion

3.1. Oscillatory rheology

The storage (elastic) modulus G′ was taken as a representative viscoelastic parameter from dynamic oscillatory measurements. Being a measure of sample resistance to elastic deformation (i.e. a reflection of the polymer network connectivity), the storage modulus has been chosen as an indicator of polymer/mucin interactions by several authors [7–12,16,17], in some cases coupled with the loss (viscous) modulus G″. Fig. 1 and Fig. 2 present the storage modulus variation with frequency for the TEA neutralised and unneutralised samples, respectively. The storage modulus curve of 10% mucin gel was included in both graphs as a reference. Since the G′ values of the mucin gel were very low (0.1 Pa at 1.129 Hz), the rheological synergy (ΔG′) was determined as the difference between the G′ values of the mixture and the respective polymer gel.

The rheological synergy was found to be a frequency-dependent parameter in the case of neutralised PAA samples (Fig. 1), with both positive and negative synergy noted, depending on the period used. The crossover point for Carbopol 974P was at approximately 4 Hz, for Noveon AA-1 near 0.4 Hz, while Carbopol 971P showed positive rheological synergy over the whole frequency range. The level of cross-linking was previously shown to be a prominent factor in the 'gel-strengthening' phenomenon between carbomers and homogenised mucus gel [16]. The same factor is probably the cause of variation in this case, with the least cross-linked Carbopol 971P having the most flexible chains, capable of high level of interaction with the mucin glycoproteins. In all three cases the positive rheological synergy increased with frequency. This finding indicates that caution should be applied when interpreting results obtained by dynamic rheological analysis of polymer/mucin mixtures, as, at least in some cases, completely different trends may be observed depending on the frequency of observation. This is further illustrated by Table 1 and Table 2, presenting the percentage increase in G′ for a series of polymers at two different frequencies, 1.129 and 6.952 Hz.

Negative synergy for the unneutralised gel systems was observed over the entire frequency range, as shown in Fig. 2. It is known that the acidic PAA hydrogels contain only slightly uncoiled macromolecules, unable to form an elastic polymer network, due to the absence of significant dissociation and the subsequent repulsion of negative charges. Their viscoelastic parameters are profoundly lower than for the neutralised gels, which is accompanied by the lower level of mucoadhesiveness [15]. The marked negative synergy found in all cases may be due to the limited propensity of the unneu-

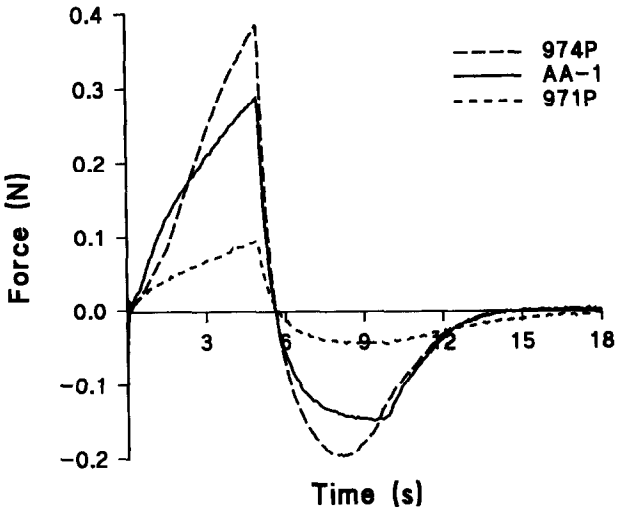

Fig. 3. Penetration/withdrawal profiles obtained by texture analyzer for the three neutralised polymer gels.

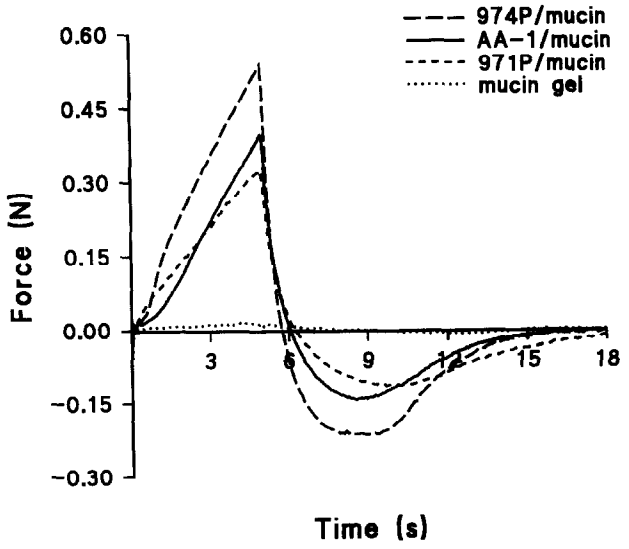

Fig. 4. Penetration/withdrawal profiles obtained by texture analyzer for the three neutralised polymer/mucin mixtures and the mucin gel.

Table 3
The percentage increase in work of cohesion, obtained as positive area under the penetration/withdrawal curve

Penetrometry data (work of cohesion)			
Sample	+Area (μJ) polymer gel	+Area (μJ) polymer/mucin mixture	% Increses
Carbopol 974P+TEA	1024.0 ± 28.5	1543.0 ± 51.5	50.7
Carbopol 974P	263.0 ± 10.7	80.9 ± 3.9	−69.2
Noveon AA-1+TEA	903.9 ± 35.0	1254.0 ± 39.8	38.78
Noveon AA-1	253.8 ± 9.9	66.3 ± 3.0	−73.9
Carbopol 971P+TEA	301.7 ± 12.1	1001.0 ± 45.2	231.8
Carbopol 971P	167.3 ± 6.1	66.3 ± 2.7	−60.4

Table 4
The percentage increase in work of adhesion, obtained as negative area above the penetration/withdrawal curve

Penetrometry data (work of adhesion)			
Sample	−Area (μJ) polymer gel	−Area (μJ) polymer/mucin mixture	% Increase
Carbopol 974P+TEA	844.0 ± 35.6	1172.0 ± 49.8	38.9
Carbopol 974P	231.0 ± 8.7	50.2 ± 2.1	−78.3
Noveon AA-1+TEA	723.4 ± 29.1	920.0 ± 40.2	27.0
Noveon AA-1	215.5 ± 10.0	49.8 ± 1.9	−76.9
Carbopol 971P+TEA	309.8 ± 11.9	793.6 ± 35.5	156.2
Carbopol 971P	163.4 ± 7.2	34.9 ± 1.3	−78.6

tralised molecules to penetrate the mucin gel. Alternatively, the results may be at least partially a reflection of the purity of the mucin used in this study. The occurrence of negative rheological synergy in PAA gels is well documented by Rossi et al., [11] with regard to different mucin samples and different aqueous media. It was concluded that the rheological interaction was strongly influenced by the mucin type, predominantly due to the presence of various ions in the mucin solutions. This was concluded on the basis that purified (dialysed) mucin samples gave a stronger rheological interaction with the PAA gel [11]. The data presented here therefore indicate that the presence of ions (which will be present in an in vivo situation) may exert a much smaller influence on the negative synergistic behaviour when the polymers are neutralised with triethanolamine.

3.2. Texture analysis

Texture analysis is a penetrometry technique that has been extensively employed in the mechanical characterisation of food materials. Recently, it has emerged as an useful technique in the field of pharmaceutical gel characterisation [18,19]. In particular, Tobyn et al. [20,21] have used the technique as a means of measuring bioadhesion. Fig. 3 presents typical penetration/withdrawal curves of the neutralised PAA hydrogels. At time 0, the cylindric probe touches the surface of the sample, whereupon it progresses 5 mm into the gel system at the speed of 1 mm/s. The maximum penetration resistance force (+peak) and the work performed (+area) along with the withdrawal parameters (−peak and −area) are readily obtained by the software provided with the instrument. The values of positive and negative areas are associated with the work of cohesion of the sample and the work of adhesion to the probe, respectively [22]. The rank order of adhesiveness and cohesiveness of the three polymer gels (Fig. 3) correlates well with the storage modulus values obtained by dynamic rheology (Fig. 1).

Fig. 4 shows the penetration/withdrawal curves of the respective mucin mixtures, along with the reference data for 10% mucin gel. The rank order of detachment forces was again identical to that found for the corresponding rheological studies. It was also noted that the withdrawal curve of 971P/mucin mix did not cross the x-axis, indicating that the 'stringiness' of this sample was such that the thin thread of the sample did not break when the probe reached a predetermined distance (10 cm) from the sample surface.

Table 3 and Table 4 present the values of positive (cohesive) and negative (adhesive) work and the percentage of its increase for the neutralised and acidic samples. The corresponding values for the maximum adhesive force (−peak) were given in Table 5. It is evident that the neutralised Carbopol 971P mix showed the largest structural synergy with regard to all three parameters. However, the rank order of adhesiveness for the three polymers (Fig. 4) was in agreement with

Table 5
The percentage increase in maximum adhesive force, obtained as negative peak of the penetration/withdrawal curve

Penetrometry data (maximum adhesive force)			
Sample	−Peak (mN) polymer gel	−Peak (mN) polymer/mucin mixture	% Increase
Carbopol 974P+TEA	198.8 ± 8.0	216.7 ± 9.9	9.0
Carbopol 974P	59.90 ± 2.1	13.0 ± 0.6	−78.3
Noveon AA-1+TEA	149.8 ± 6.9	157.3 ± 6.5	5.0
Noveon AA-1	44.15 ± 1.5	9.6 ± 0.4	−78.2
Carbopol 971P+TEA	43.1 ± 2.0	117.4 ± 5.0	172.4
Carbopol 971P	28.0 ± 1.4	9.0 ± 0.3	−67.9

the storage modulus values of the polymer/mucin mixtures (Fig. 1). All unneutralised samples showed negative synergy when mixed with mucin during texture studies (Tables 3–5), confirming the results of oscillatory rheology tests (Fig. 2). Fig. 5 shows the penetration/withdrawal profiles of a representative sample, Carbopol 974P, in its pure form and in the mixture with mucin, along with the mucin gel.

A relationship was found between the phase angle δ at 1.129 Hz obtained from oscillatory rheology and both the positive and negative areas obtained from texture analysis (work of cohesion and adhesion); the

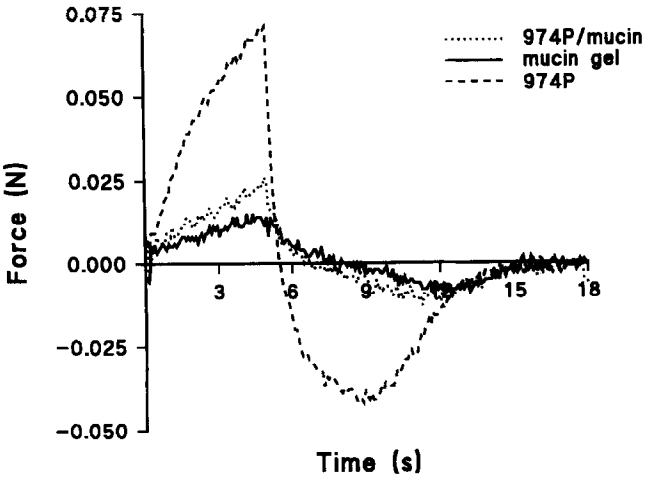

Fig. 5. Penetration/withdrawal profiles obtained by texture analyzer for the unneutralised Carbopol 974P gel, the mucin gel and their mixture.

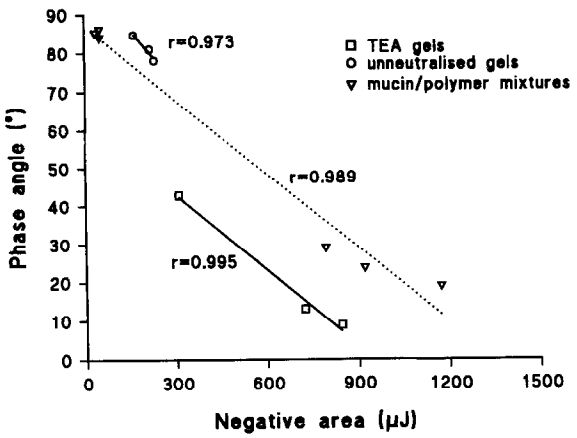

Fig. 6. Correlation between viscoelastic parameter (phase angle) and texture analysis parameter (negative area) for the polymer gels and polymer/mucin mixtures.

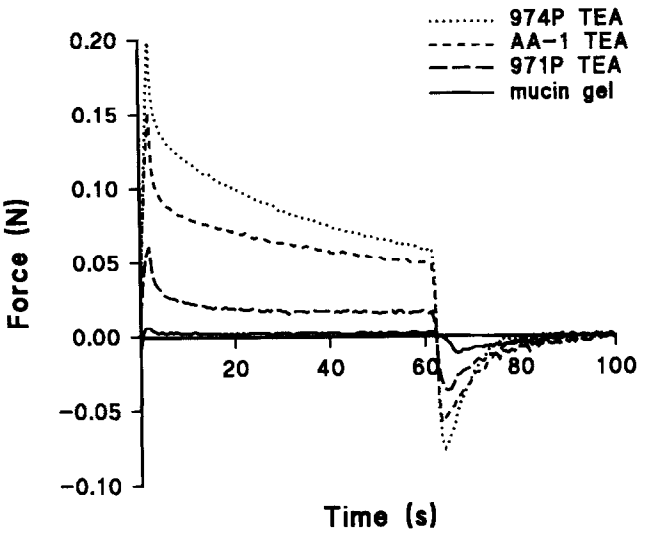

Fig. 7. Tensile test profiles for the neutralised polymer gels and the mucin gel.

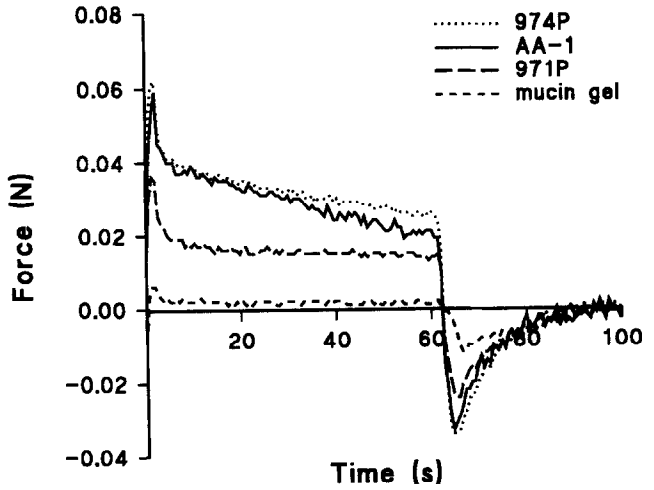

Fig. 8. Tensile test profiles for the unneutralised polymer gels and the mucin gel.

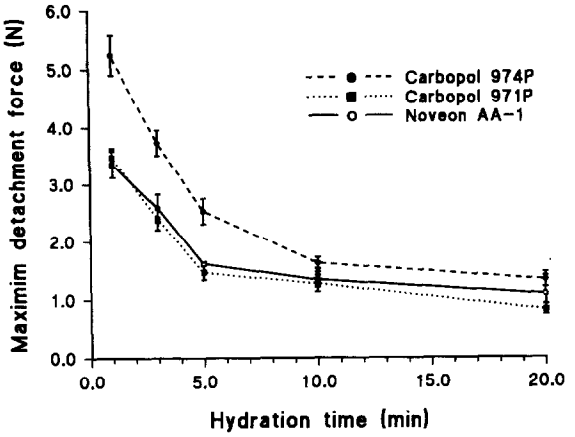

Fig. 9. Influence of the hydration time on the maximum detachment force for the polymer compacts.

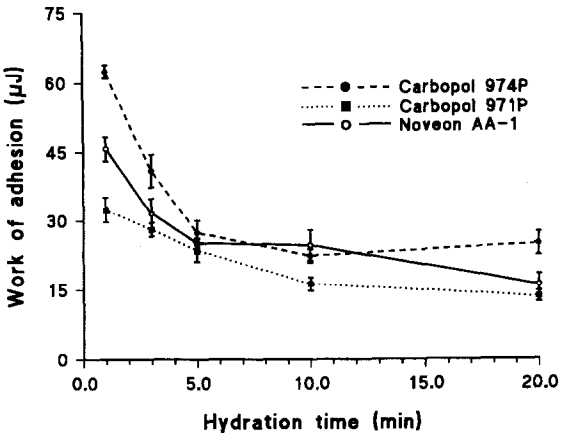

Fig. 10. Influence of the hydration time on the work of adhesion for the polymer compacts.

latter is presented in Fig. 6, along with the regression coefficients for each curve. This confirms the existence of reasonable linear correlation between a viscoelastic and a penetration parameter, but only if very similar structures are considered.

3.3. Tensile tests

Despite the problems associated with tensile mucoadhesive techniques, this approach is the most widely used in the bioadhesion field. The use of solid mucoadhesive dosage forms (films, patches, tablets, coated micro spheres, etc.) dominates in tensile testing, since it is known that the adhesiveness decreases rapidly when certain levels of hydration are achieved. However, there is also a need to test partially hydrated polymers, at least in order to investigate semisolid mucoadhesives. A further, more general consideration is that gel formation is an inevitable step in mucoadhesion, hence there is a need to study the processes associated with polymer-mucin gel interactions. Indeed, the concept of studying aqueous polymer gels in order to simulate the outer surface of a hydrated tablet has been previously explored [23].

Fig. 7 shows detachment profiles of the neutralised carbomer and polycarbophil gels. The initial maximum relates to the probe being moved into the gel surface, while the ensuing positive sections of the curve reflect the sample resistance to the constant force exerted by the mucin-covered probe; the negative section is related to the detachment of the two systems. Rupture of the gels occurred in the mucin layer in all cases. It is interesting to note the demonstration of viscoelastic behaviour of the three sets of hydrogels, with resistance to the external force declining over time (Fig. 7). The rank order of resistance to the probe and adhesiveness complied with the information obtained by rheology and texture analysis of the gels alone, with the same rank order between polymers being noted for all studies. The corresponding graph showing unneutralised samples is presented in Fig. 8, with smaller detachment forces noted. The results disagree with the finding of negative synergy obtained previously, since the three acidic hydrogels showed a certain, albeit small, level of mucoadhesiveness.

The results of the study on polymer compacts, in the form of maximum detachment force and work of adhesion, are shown in Fig. 9 and Fig. 10, respectively. Both parameters indicated that Carbopol 974P showed the greatest adhesion to the mucin surface and Carbopol 971P the least, with Noveon AA-1 being approximately intermediate between the two; again, this is the same rank order as was found with the rheological and tensile tests. The same rank order of adhesiveness for the three PAA resins obtained in this study (Carbopol 974P > Noveon AA-1 > Carbopol 971P) has been reported by B.F. Goodrich, using a force of 10 PSI, a contact time of 2 s and a 1.2% polymer gel in water (pH 4.5) tested against a plastic surface [24].

It was also noted that the bioadhesion decreased with prehydration time. In a previous study, a decrease in mucoadhesive bond strength with the (pre)hydration time was reported for Carbopol 934P tablets to gastric tissue [20] with the pattern of larger fall during the first 5 min, which corresponds very well with our findings. However, Ponchel et al., [25] found a maximum work of adhesion after 10 min of hydration for compacts containing 50% PAA and 50% HPMC. The fall in mucoadhesiveness, which followed this maximum, was explained as a result of possible further water diffusion towards the rest of the dry tablet and the drying out of the bioadhesive interface [25]. It is possible that a similar process has occurred in our systems only on a more rapid timescale, so that after only 1 min a decrease was observed. It appears that the three samples have reached a quasi-equilibrium state after 10 min, showing only small changes in mucoadhesive performance with further swelling (Fig. 9 and Fig. 10).

4. Conclusions

This study has been concerned with the comparison of different in vitro methods for studying mucoadhesion. Dynamic oscillatory rheology and texture analysis were used to measure the bulk properties of the polymer/mucin mixtures relative to the polymer alone, while tensile techniques have provided data on the force and work of detachment between polymer gels or compacts and a layer of mucin gel.

It was found that all the methods revealed the same rank order of both strength and mucoadhesiveness for the three PAA polymers, i.e. Carbopol 974P > Noveon AA-1 > Carbopol 971P. Studies investigating the rheological behaviour of polymer/mucin mixes indicated firstly that the synergy observed is highly frequency dependent and secondly that neutralised Carbopol 971P showed the greatest evidence for positive synergy. Texture analysis studies indicated the same trend in that the rank order given above was seen for the PAA gels alone and for the PAA/mucin mixes, although again Carbopol 971P showed the greatest evidence for synergy. A correlation was found between the rheological and texture analysis data. Detachment studies again showed the rank order given above, both using PAA gels and partially hydrated tablets. The data presented here indicate that, at least under the experimental conditions used in this study, the rheological behaviour of the bioadhesive gel is a highly important factor in determining mucoadhesion. It is also interesting that the PAA polymer that showed the greatest evidence for molecular interaction with the mucin (neutralised Carbopol 971P) also showed the weakest bioadhesion. This must be considered in conjunction with previous studies such as that by Ponchel et al., [26], who discussed a model whereby the strength of the mucoadhesive bond is considered to be a function of both the interaction energy between the adhesive and the mucosa and the viscoelastic properties of the interfacial layer formed between the two surfaces. The results of the force of detachment tests used in the present study are therefore almost certainly a function of numerous processes within the polymer-mucin systems; the data reported here indicate that the rheological properties of the polymers themselves are an integral component to the detachment process.

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