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The Effects of Ageing on the Rheological, Dielectric and Mucoadhesive Properties of Poly(Acrylic Acid) Gel Systems

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Purpose. The purpose of this study was to investigate the effects of storage on the physical properties of a series of poly(acrylic acid) (PAA) hydrogels, using two dynamic techniques, oscillatory rheology and dielectric spectroscopy. Furthermore, the effects of ageing on the mucoadhesive properties were evaluated and related to the changes in structure.

Methods. Three carbomers (Carbopols 934P, 974P and EX-214) and polycarbophil (Noveon AA-1) have been formulated as hydrogels with a range of neutralising agents (NaOH, triethanolamine and tromethamine). The effects of storage for six months on the gel structure were measured using oscillatory rheology and low frequency dielectric analysis. Mucoadhesive performance was studied by means of a detachment force test.

Results. A substantial decrease in the rheological storage moduli was noted for all samples, while the tan δ values remained unchanged for the majority of systems. Dielectric studies revealed that gels neutralised with triethanolamine showed a greater degree of binding of neutralising ions to the gel network than did the other two agents. It was also found by the dielectric analysis that, on storage, the distribution of ions within the gel systems changed. This may be due to the neutralising ions being liberated from the gel network into the bulk aqueous phase, thereby contributing to the decrease in rheological storage modulus. Mucoadhesion studies indicated that, despite the substantial changes in gel structure, there was no alteration in the bioadhesive force of detachment for the majority of systems during a six month period.

Conclusions. A redistribution of cations between the polymer cluster and the bulk of medium is proposed as an possible additional mechanism of ageing of PAA hydrogels. The results obtained support the hypothesis outlined previously that the mucoadhesive strength is related to the tan δ value rather than the viscosity of the gel.

KEY WORDS: carbomer; dielectric; hydrogel; mucoadhesion; polycarbophil; rheology.

INTRODUCTION

Bio(muco)adhesive dosage forms have been studied extensively due to their potential importance in controlled drug delivery applications (eg. 1). In particular, these systems are used to prolong (and ideally to control) the contact time between a dosage form and an adsorbing membrane.

Mucoadhesive polymers are generally hydrophilic macromolecules which contain numerous hydrogen bond forming groups and which will hydrate and swell when placed in contact with an aqueous solution. Poly(acrylic acid) (PAA) polymers are well established as good mucoadhesives (2). They are long-chain, high molecular-weight, cross-linked polymers, composed of carboxyvinyl groups. When placed in water, PAA polymers behave as anionic polyelectrolytes and form weak hydrogel structures. In the presence of neutralising agents, a stable three-dimensional viscoelastic network is formed. Two mechanisms are considered to be responsible for the formation of the more rigid gel structures on addition of neutralising agents: enhanced repulsion of negative charges along the polymer backbone and higher osmotic pressure inside the swelling polymer, both due to the greater degree of dissociation of carboxyl groups upon the addition of a base.

In a previous study (3), we have used two dynamic techniques in conjunction, namely oscillatory rheology and dielectric spectroscopy, to assess the structure of freshly prepared PAA hydrogels. The aim of the present study was to examine the effects of ageing on the structure of a range of PAA gel systems and to relate any observed changes to mucoadhesive performance. The ageing behaviour of these hydrogels has not been studied in detail thus far; it is known that the viscosity of gels generally tends to decrease over time due to the elastic contraction of polymer molecules (4), the extreme result of that process being syneresis. Furthermore, PAA systems are susceptible to catalytic degradation, induced by UV light or traces of iron and other transition metals, which in turn reduces the gel viscosity (5). It is therefore of interest to monitor the changes in physical structure and characteristics of the hydrogel systems over time using the novel approach described above. It is also essential to determine and quantify the effects of storage on product performance in order to formulate and develop bioadhesive dosage forms.

MATERIALS AND METHODS

Materials

Three bioadhesive carbomer resins (Carbopol 934P, Carbopol 974P and Carbopol EX-214, B.F. Goodrich, USA) were used throughout the study. These materials are homopolymers of acrylic acid ($CH_2 = CH - COOH$), cross-linked with either allylsucrose or allylpenthaerythritol (5). Carbopol EX-214 is the sodium salt of 974P and does not require neutralisation upon mixing with water.

In addition to the carbomers, a polycarbophil resin (Noveon AA-1, B.F. Goodrich, USA) was assessed, this being a PAA polymer cross-linked with divinylglycol (5). Triethanolamine (TEA, Sigma, UK), tromethamine (TRIS, Sigma, UK) and sodium hydroxide (BDH, UK) were used as neutralising agents. Mucin type III (partially purified from porcine stomach, Sigma, UK) was used as a mucous substrate. Double distilled water was used for all experiments.

Methods

The method of gel preparation has been described in detail previously (3). All the neutralised systems (and Carbopol EX-214) were in the pH range of 6.8 to 7.2, while the unneutralised gels were acidic (pH 3.1 to 3.2). The samples were placed in airtight plastic containers, protected from light and stored at room temperature (25 ± 3°C) for six months.

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Rheological properties of the PAA gels were evaluated using a controlled-stress rheometer (Carri-med CSL 500, TA Instruments Ltd., U.K.), over a frequency range of 0.01 to 10 Hz at 25°C. Dielectric studies were conducted using a Dielectric Spectrometer (Dielectric Instrumentation Ltd., U.K.) over a frequency range of 10^{-2} to 10^{4} Hz at 25°C. More details concerning the experimental procedures, as well as the theoretical basis behind the use of these two dynamic techniques has been outlined in the previous studies (3, 6).

Mucoadhesive properties of the PAA hydrogels were determined *in vitro* using Dynamic Contact Angle Analyzer (DCA-312, Chan Instrumentation Inc., USA). Porcine gastric mucin in the form of 30% w/w gel in water was employed as a mucous substitute (3).

RESULTS AND DISCUSSION

The Effects of Ageing on the Rheological Properties

The parameters characterising the rheological behaviour of the freshly prepared PAA gel systems (elastic modulus G' and the tan δ, at the representative frequency of 0.5456 Hz) are presented in Table I. The storage (elastic) modulus G' is a measure of the energy stored and recovered per cycle of deformation and reflects the solid-like component of viscoelastic behaviour, as opposed to the viscous (loss) modulus G'', which reflects liquid-like behaviour (7). The elastic modulus is known to be closely related to the connectivity of the polymeric network; quantitatively G' is directly proportional to the number of entities which can support stress, i.e. elastically active network chains (8). The ratio of viscous to elastic moduli is known as loss tangent (tan δ) and is a useful parameter in describing the overall elasticity of the sample (8). Since $\tan \delta = G''/G'$, a higher numerical value for tan δ indicates a lower degree of elasticity of the material.

The rank order of G' with respect to the various neutralising agents is in good agreement with the results of Lochhead et al (9), who stated that the hydrodynamic volume of the polymer network was inversely proportional to the neutralising base strength. Furthermore, the values of G' were considerably lower for the neutralised Noveon AA-1 (polycarbophil) gels than for the two carbomers, which is due to differences in gel structure (3).

Table II shows the same parameters obtained after a six month storage period. More than a three fold decrease in elastic modulus was noted for all the neutralised hydrogel samples. Carbopols 934P and 974P revealed very similar storage moduli in the fresh state, followed by more marked differences after ageing (Figure 1). No major differences in viscoelasticity between fresh and aged gels were found, as seen by comparing the tan δ values in Tables I and II. This is due to the fact that the viscous modulus (G'') has also decreased considerably, leaving the ratio G''/G' almost unaltered. The main changes occurred in the case of NaOH neutralised and the unneutralised samples, showing lower tan δ values (i.e. higher overall elasticity) after ageing.

The tan δ values of two sodium neutralised systems are shown in Figure 2. Carbopol EX-214 has a considerably lower elastic modulus than its chemical equivalent, Na neutralised Carbopol 974P (Table I), which has been attributed to different degrees of ionisation between PAA (in 974P) and PAA-Na (in EX-214) (10). The differences in structure between these two supposedly identical systems is shown in terms of the tan δ values over three decades of frequency for fresh and aged gels.

Unneutralised samples have shown significantly weaker gel networks, as expected, due to the constricted gel network. Examined rheologically under the same conditions as neutralised samples, they showed almost no elasticity in the region of 0.01 to 1 Hz, hence the data obtained at 1.129 Hz were included in Tables I and II. After ageing, their tan δ values have decreased (elasticity increased), possibly due to the formation of additional hydrogen bonds over time.

The Effects of Ageing on Dielectric Properties

The use of low frequency dielectric spectroscopy in the characterisation of Carbopol gels has been outlined in previous

Table I. Rheological, Dielectric and Mucoadhesive Parameters of Freshly Prepared PAA Hydrogels (m ± sd)

Sample	G' at 0.5456Hz (Pa)	tan δ at 0.5456Hz	G/ω at 0.1Hz (10^{-5}F)	G/ω at 10^4Hz (10^{-7}F)	Detach. force (mg)
Carbopol 934P					
NaOH	929 ± 38	0.134 ± 0.001	0.66 ± 0.08	7.43 ± 0.36	3973 ± 300
TEA	1005 ± 7	0.125 ± 0.001	1.77 ± 0.14	5.89 ± 0.36	4277 ± 410
TRIS	948 ± 7	0.129 ± 0.001	0.76 ± 0.08	4.87 ± 0.23	4290 ± 342
unneutr.	0.3 ± <0.1*	12.18 ± 0.52*	1.14 ± 0.13	1.21 ± 0.09	1127 ± 51
Carbopol 974P					
NaOH	888 ± 25	0.200 ± 0.012	1.07 ± 0.02	6.50 ± 0.39	4093 ± 150
TEA	939 ± 12	0.159 ± 0.001	2.15 ± 0.15	5.62 ± 0.29	4289 ± 266
TRIS	901 ± 90	0.178 ± 0.023	0.87 ± 0.13	3.59 ± 0.18	4226 ± 149
unneutr.	9.5 ± 1.8*	3.68 ± 0.37*	1.02 ± 0.10	1.11 ± 0.07	1949 ± 92
Noveon AA-1					
NaOH	459 ± 19	0.286 ± 0.045	0.82 ± 0.06	8.11 ± 0.55	3113 ± 225
TEA	441 ± 18	0.236 ± 0.005	2.09 ± 0.08	7.87 ± 0.35	3237 ± 166
TRIS	416 ± 15	0.254 ± 0.020	1.06 ± 0.12	6.81 ± 0.32	3336 ± 183
unneutr.	3.7 ± 1.0*	6.44 ± 1.13*	0.73 ± 0.03	1.02 ± 0.06	1936 ± 175
Carbopol EX-214	426 ± 8	0.602 ± 0.037	1.30 ± 0.10	7.34 ± 0.29	3291 ± 124

* Data taken at 1.129 Hz.

Table II. Rheological, Dielectric and Mucoadhesive Parameters of PAA Hydrogels after Six Months of Storage (m ± sd)

Sample	G′ at 0.5456Hz (Pa)	tan δ at 0.5456Hz	*G*/ω at 0.1Hz (10^{-5}F)	*G*/ω at 10^4Hz (10^{-7}F)	Detach. force (mg)
Carbopol 934P					
NaOH	315 ± 1	0.107 ± 0.002	0.96 ± 0.04	8.67 ± 0.34	4341 ± 143
TEA	268 ± 5	0.128 ± 0.003	1.05 ± 0.05	6.60 ± 0.32	4200 ± 252
TRIS	270 ± 1	0.130 ± 0.002	0.83 ± 0.06	5.88 ± 0.22	4220 ± 602
unneutr.	0.3 ± <0.1*	7.16 ± 0.51*	0.86 ± 0.04	1.38 ± 0.03	1291 ± 25
Carbopol 974P					
NaOH	243 ± 1	0.155 ± 0.001	0.70 ± 0.03	7.62 ± 0.21	4368 ± 218
TEA	282 ± 4	0.160 ± 0.009	1.72 ± 0.06	6.85 ± 0.20	4300 ± 320
TRIS	269 ± 18	0.155 ± 0.002	0.66 ± 0.05	4.16 ± 0.15	4407 ± 401
unneutr.	7.3 ± 0.7*	2.96 ± 0.27*	0.71 ± 0.03	1.27 ± 0.06	1996 ± 82
Noveon AA-1					
NaOH	122 ± 6	0.246 ± 0.013	0.88 ± 0.02	10.69 ± 0.65	3252 ± 251
TEA	134 ± 3	0.239 ± 0.006	1.33 ± 0.06	11.27 ± 0.61	3184 ± 302
TRIS	113 ± 9	0.276 ± 0.018	0.97 ± 0.04	8.01 ± 0.39	3423 ± 149
unneutr.	4.1 ± <0.1*	2.86 ± 0.11*	1.26 ± 0.06	1.21 ± 0.05	1971 ± 104
Carbopol EX-214	121 ± 6	0.530 ± 0.015	0.65 ± 0.04	9.44 ± 0.37	3644 ± 199

* Data taken at 1.129 Hz.

studies (3,6). Dielectric analysis usually involves the application of a sinusoidal electric field to a sample and the measurement of the response (polarisation) of that material. The two components of the response may be expressed in terms of the capacitance C and dielectric loss *G*/ω (where *G* is the conductance at an angular frequency ω).

It was previously suggested (3,6) that the dielectric response of Carbopol hydrogels over a frequency range of 10^4 to 10^{-2} Hz comprises two regions. The higher frequency region corresponds to a process dominated by the conductivity of the bulk liquid (i.e. the movement of charges through the gel network). The lower frequency response corresponds to the presence of a gel layer on the electrodes, through which charges may pass, but with greater difficulty than through the bulk liquid. In general, therefore, rheological studies give an indication of the behaviour of the polymer chains in gel systems, while dielectric analysis yields information on the movement of charges through the gel network.

Dielectric loss values of the fresh samples at the representative low (0.1 Hz) and high frequency (10^4 Hz) are shown in Table I. The TEA neutralised systems showed the highest low frequency response; this indicates the presence of a greater number of charges in the barrier layer (i.e. the vicinity of the polymer) in these hydrogels compared to NaOH or TRIS neutralised systems. It is known that the fraction of bound counterions (the cations trapped in the electrostatic field of the PAA polyion) in the case of Na^+ and K^+ ions is around 60% (11). The dielectric loss data (Table I) suggests that the binding ability of TEA cations to PAA polyions is larger than those of TRIS and Na ions. This correlates with the observation that,

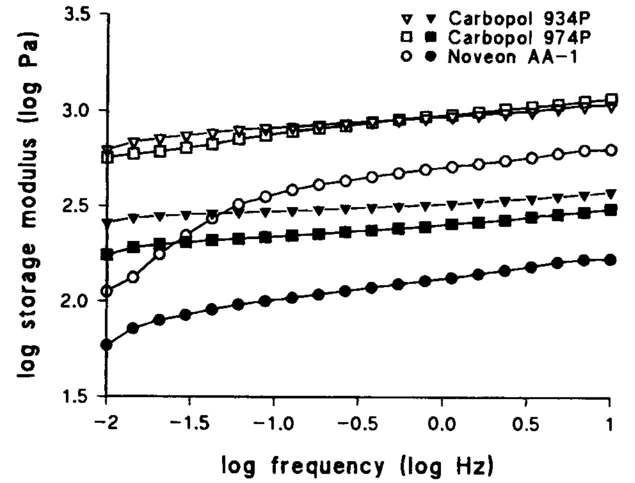

Fig. 1. Variation of the rheological storage modulus with frequency for a range of poly(acrylic acid) gels neutralised with sodium hydroxide, in the fresh (open symbols) and aged state (solid symbols).

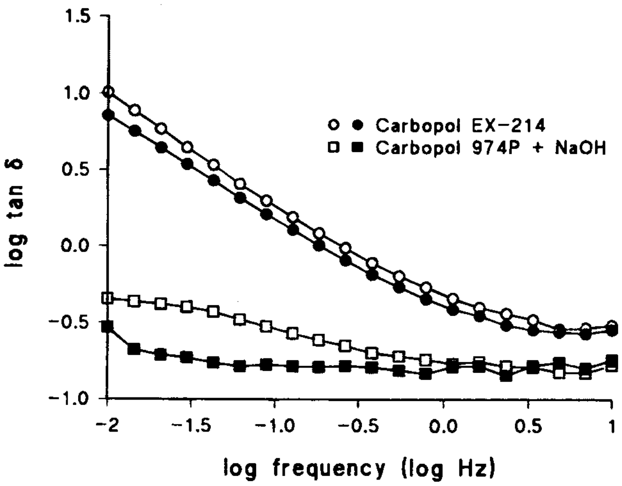

Fig. 2. Variation of the rheological tan δ value with frequency for fresh (open symbols) and aged (solid symbols) Carbopol EX-214 gels and Carbopol 974P gels neutralised with sodium hydroxide.

in general, the highest G′ and lowest tan δ values were observed for TEA neutralised hydrogels, indicating a higher degree of polymer chain expansion.

Table II shows the equivalent dielectric data after six months storage. Figure 3 shows the dielectric spectra for TEA neutralised Noveon AA-1 gels, with the low frequency (electrode gel layer) and high frequency (bulk conductivity) responses being observed below and above approximately 10^3Hz respectively. While the low frequency loss decreased on storage, the high frequency response increased. Similarly, as shown in the Tables I and II, the dielectric loss values of all the aged samples in the high frequency region were found to be higher than for the fresh ones, especially for the neutralised samples. These results therefore suggest that charge-carrying species have been released from the vicinity of the polymer into the bulk, either as a result of chemical degradation or changes in the neutralisation/dissociation equilibrium. Ion-exchange equilibrium considerations are known to be very important for the properties of ionic hydrogels, along with polymer-solvent and polymer-ion interactions, since they directly influence the swelling characteristics of polyelectrolytes (12). This mechanism is also compatible with the observed decrease in G′ seen on storage, as the release of neutralising ions from the bound state into the bulk aqueous phase may be expected to result in a decrease in polymer chain ionisation and hence expansion, leading in turn to a lower elastic modulus. Dielectric analysis has therefore suggested an additional mechanism of ageing, i.e. a partial dissociation of the polyion-base salt over time.

The Effects of Ageing on Mucoadhesive Performance

Maximum detachment forces for the fresh PAA hydrogels are shown in Table 1. The significantly lower values obtained for the unneutralised samples compared to the neutralised ones do not support the assumption that adhesive gels of lower viscosity can make closer contact with the surface and so achieve better bioadhesion (13). In fact, the data obtained suggest that there is a relationship between viscoelastic properties of hydrogels and their bioadhesive performance, which has been previously suggested by Caramella et al, (14) as well as our previous work (3). In particular, tan δ values correlate with maximum detachment forces in an inverse manner (Table I). The results obtained after a six month ageing period provide further evidence for the existence of such a relationship (Table II). As discussed previously, all Na neutralised samples have shown lower tan δ values after ageing, indicating an increase in overall elasticity compared with TEA and TRIS samples (which may be due to the fact that inorganic PAA salts possess slightly higher resistance to catalytic degradation than the organic ones (5)). Indeed, this trend corresponds very well with the increase in the maximum detachment force in Na hydrogels after ageing.

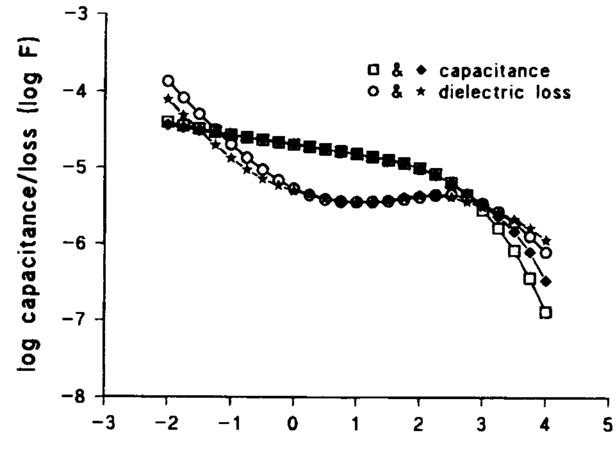

Fig. 3. Low frequency dielectric response of fresh (open symbols) and aged Noveon AA-1 gels (solid symbols) neutralised with triethanolamine.

CONCLUSIONS

The study has demonstrated that PAA hydrogels may undergo significant changes in structure on storage and that these changes may be usefully monitored by using rheological and dielectric analysis in conjunction. The investigation has indicated that in addition to the accepted mechanisms such as catalytic degradation of the polymer chains, these ageing effects may be due to changes in the distribution of neutralising ions within the gel, with those ions being released from the immediate vicinity of the polymers chain into the bulk aqueous phase. The study has also lent further support to the hypothesis that the bioadhesive strength is related to the tan δ value, rather than to the absolute values of the storage or loss moduli, as neither the force of detachment nor the tan δ value changed significantly on storage for the majority of systems, despite the considerable changes observed for the two moduli.

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