European Journal of Pharmaceutics and Biopharmaceutics 44 (1997) 61–70

# Dielectric analysis of bioadhesive gel systems[1]

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Received 8 January 1997; accepted 24 February 1997

## Abstract

Dielectric spectroscopy is an analytical technique which involves the application of an oscillating electric field to a sample and the measurement of the corresponding response over a range of frequencies, from which information on sample structure and behaviour may be extrapolated. This method has recently been applied to a number of pharmaceutical systems, including bioadhesive gels. In this review, the principles of the technique will be outlined, followed by a discussion of work that has been conducted to date on bioadhesive systems. In particular, studies on sodium alginate gels will be described whereby a model was proposed in order to relate the low frequency response to the gel structure. Studies on cross-linked polyacrylic acids will then be outlined, including investigations into the effects of additives such as propylene glycol and chlorhexidine gluconate, the influence of the choice of neutralising agent and the effects of ageing on the gel structure. © 1997 Elsevier Science B.V.

*Keywords:* Alginate; Bioadhesion; Chlorhexidine gluconate; Diclofenac sodium; Dielectric; Polyacrylic acid; Rheology

## 1. Introduction

Bioadhesive dosage forms have generated considerable interest in recent years as means of providing extended dosage form residence time, localising drug delivery in specified regions and providing intimate contact with an absorbing membrane, with the ultimate view of improving drug bioavailability [1]. More recently, there has been focus on certain physiological properties of bio(muco)adhesive polymers such as the inhibition of proteolytic enzymes and the induction of increased epithelial permeability, these being of particular interest in the field of protein/peptide delivery [2]. Consequently, a wide range of approaches have been adopted in order to study the potential efficacy of hydrophilic polymers as bio- or mucoadhesives, largely centering around the measurement of the adhesion of bioadhesive polymers to ex vivo tissue or mucin surfaces, usually by force of detachment tests. However, such approaches inevitably involves certain inherent difficulties, notably the choice of substrate, the method of detachment from the surface and the physical form of the bioadhesive polymer. For example, several studies have indicated that the force of detachment of a bioadhesive polymer may be largely associated with the viscoelastic properties of the polymer itself, rather than necessarily a specific interaction with mucin (e.g. [3]). There is therefore a strong necessity for a greater understanding of the gel properties of the bioadhesive polymers themselves.

While much of the literature relating to bioadhesion describes the functionality of the polymer systems as potential dosage forms, less information is available on the polymeric gel structure, hence it has proved difficult to associate the properties of the gel to bioadhesive performance. This is largely because, despite the apparent chemical simplicity of these gels, there is a paucity of techniques available for characterising the physical

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[1] In part presented at the 2nd Rencontre-Pharmapeptides, held on October 3–4, 1996 at the Center Interuniversitaire de Recherche et d'Enseignement, Archamps, France.

*PII* S0939-6411(97)00102-1

structure of these systems. The techniques that have been used to study both the gels themselves and their interaction with mucin [4] include rheological tests [5,6] and ATR-FTIR [7]. In this review, the use of dielectric analysis as a further means of characterising the structure of bioadhesive gels will be described. This technique has been extensively used in the physics, colloid and polymer sciences, but has only recently been used in the study of pharmaceutical systems [8]. The principles behind the technique, the applicability of the method to gel systems and the work to date on the study of bioadhesive polymers will be described.

### 1.1. Principles of dielectric analysis

Dielectric analysis involves the application of a sinusoidal electric field to a sample and the measurement of the corresponding response over a range of frequencies. In the simplest case, one can consider the sample to be composed of a set of dipoles which will reorientate with the field, thereby generating a polarisation current. The efficiency of this dipolar response will be frequency dependent; at any frequency, some energy will be stored by the system in the form of the reorientation process while some energy will be lost as heat.

The nature and significance of the dielectric response can be best visualised by considering the polarisation ($P$) generated in a sample subjected to a unidirectional field of magnitude $E$, given by

$$P = (\epsilon_r - 1)\epsilon_0 E \tag{1}$$

where $\epsilon_r$ is the relative permittivity (dielectric constant) and $\epsilon_0$ is the permittivity of free space, which has a constant value. In an alternating field, the polarisation will be frequency dependent and may be given by

$$P^*(\omega) = \epsilon_0 i\chi^*(\omega)\, E^*(\omega) \tag{2}$$

where $P^*(\omega)$ and $E^*(\omega)$ are the polarisation and field at frequency $\omega$, while $\chi$ is the susceptibility of the sample, which is an intrinsic property of the material and hence contains information on the material structure and behaviour. As it is necessary to consider both the magnitude and phase behaviour of the response, it is convenient to express the susceptibility as a complex variable (denoted by *), i.e.

$$\chi*(\omega) = \chi'(\omega) - i\chi''(\omega) \tag{3}$$

where $\chi'(\omega)$ and $\chi''(\omega)$ are the real and imaginary components of the susceptibility and are a reflection of the energy stored and lost within the system, respectively. The susceptibility is mathematically related to the permittivity, which is often used in the dielectric literature, given by

$$\epsilon^*(\omega) = \epsilon'(\omega) - i\epsilon''(\omega) \tag{4}$$

with the relationship between the two parameters given by

$$\epsilon^*(\omega) = \epsilon_0\{1 + \Sigma\chi'(\omega)\} - i\Sigma\chi''(\omega) \tag{5}$$

The real and imaginary susceptibilities may not be measured directly; instead, a number of pairs of extrinsic parameters may be assessed. For the purposes of the following discussion, the capacitance C and dielectric loss ($G/\omega$, where $G$ is the conductance) will be described, although several other equivalent parameters may also be measured. The capacitance and loss are related to the real and imaginary susceptibilities via

$$C(\omega) = \frac{A\epsilon_0}{\mathrm{d}}(\chi'(\omega) + \epsilon(\infty)) \tag{6}$$

and

$$G/\omega(\omega) = \frac{A\epsilon_0}{\mathrm{d}}\chi''(\omega) \tag{7}$$

These two parameters are measured over a range of frequencies, thereby generating a spectrum from which information on the structure and behaviour of the sample may be obtained by observing both the absolute magnitude of the parameters and the shape of the spectral curve. In addition to the symbols given above, the capacitance and loss are also sometimes written as $C'$ and $C''$.

Dielectric measurements have been extensively used to assess the electrical properties of sample such as semiconductors, while temperature-scanning analysis has been widely used in the polymer science field. For example, the technique has been used for detecting glass transitions and monitoring cross-linking reactions [9].

The use of this type of analysis in the study of pharmaceutical systems is comparatively recent. In terms of the type of information obtained, the method is probably analogous to rheological and thermal measurements in that it is not particularly effective in identifying specific chemical structures but is instead more useful when one is already aware of the chemical composition of the sample but wishes to know more regarding the physical structure of the systems under study. Clearly, there are many more aspects to the theoretical interpretation of the data than can realistically be presented here; the interested reader is referred to one of a number of texts on the topic [8–11].

### 1.2. The low frequency dielectric response

Dielectric analysis is unusual in that responses of interest may take place over a very wide frequency range (between $10^{-4}$ and $10^9$ Hz); no single instrument can reliably cover this range, hence a number of instruments are available, each with different measuring capabilities. The work described in this review covers the

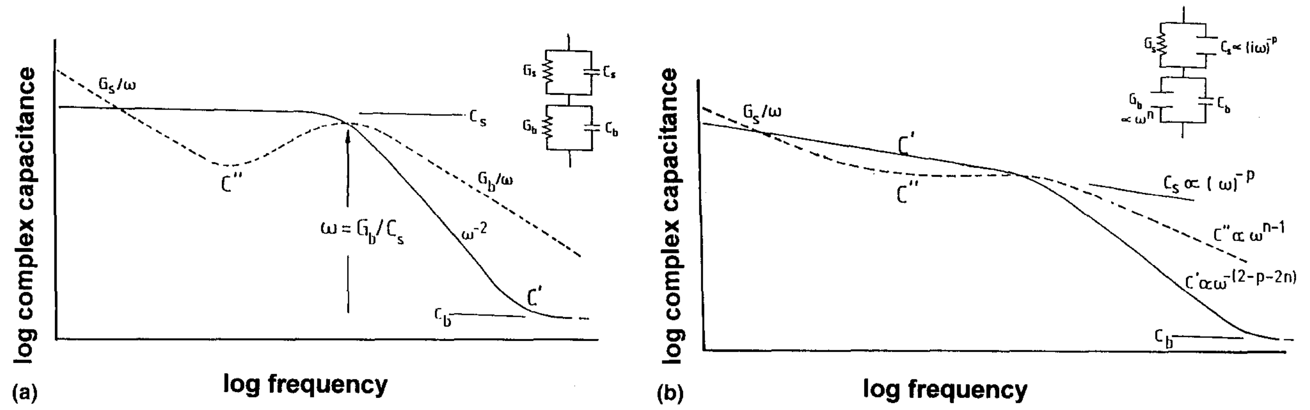

Fig. 1. Schematic representation of the Hill and Pickup [12] model for the low frequency dielectric response of a two-phase system, including equivalent circuit model showing surface (s) and bulk (b) responses. (a) ideal case; (b) real case, showing power law behaviour given by indices *n* and *p*. Adapted from [15] with permission.

measuring range between approximately $10^{-2}$ and $10^5$ Hz (i.e. kHz and sub-kHz range). The dielectric response in this region has been extensively studied by the group of Hill (e.g. 10) and a model for liquid and semi-solid systems has been developed [12]. The 'low frequency' (sub-kHz) response is considered to be a reflection of two layers within the sample, as indicated in Fig. 1. The higher frequency layer is dominated by the conductivity of the sample (the bulk response); in the scenario depicted in Fig. 1a, the conductance *G* is constant (as the gradient of the log–log plot of loss against frequency is $-1$). The response at lower frequencies is a reflection of the behaviour of a layer of sample adsorbed at the electrode surface. This surface (barrier) layer predominantly acts as a charge blocking layer, as depicted by the constant, frequency-independent capacitance; the layer can therefore be thought of primarily as a capacitor in which charge is stored. The loss slopes reflect the conductance of the barrier and bulk layers at low and high frequencies respectively, with a response being seen at intermediate frequencies which reflects the change in dominance of the bulk and barrier loss processes as the frequency increases or decreases.

The above scenario refers to systems which behave effectively ideally. In a real situation, one may observe deviations from this situation. For example, one may observe frequency dependence of the low frequency capacitance or non-unity slopes for the dielectric loss, as shown in Fig. 1b. These deviations may themselves contain information regarding the sample. In particular, the slope of the capacitance is a reflection of the 'leakiness' of the barrier layer, hence in physical terms the slope may be a reflection of the integrity of this layer. It is also worth noting that the model predicts that the values of the low and high frequency capacitance slopes will equal $-2$. Similarly, deviations from loss slopes of $-1$ indicate that the charge transport process is no longer d.c. in nature. In most aqueous systems, one would expect the conductance of the system to be due to linear charge movements through a continuous medium. In certain circumstances, however, the charge transport mechanism may be such that the ions or electrons move between certain allowed sites within the bulk of the sample, so called charge-hopping. This is a function of structuring within the systems resulting in some form of tortuosity of the charge mobility path. Deviations from negative unity slope may therefore indicate some form of network formation within the system.

## 2. Dielectric analysis of bioadhesive systems

### 2.1. Dielectric characterisation of alginate systems

Alginates are polysaccharides derived from brown algae and comprise D-mannuronic (M) and L-guluronic acid (G) residues joined linearly by 1,4 glycosidic linkages. These materials have found numerous applications in the pharmaceutical sciences, including raft forming systems, controlled release systems, tablet disintegrants, suspending agents, wound dressings and implants. In addition, these materials have been reported to be reasonably effective bioadhesives [13,14].

The dielectric response of a series of sodium alginate solutions has been studied by Binns et al. [15]. Fig. 2 shows the response of a 1% sodium alginate solution in comparison with water. Examination of the alginate spectrum shows differences between the low and high frequency responses of five orders of magnitude, this being a reflection of the different thicknesses of the bulk and surface layers. If one assumes that the permittivity of both layers is approximately equal, the surface layer may be calculated to be in the order of 10 nm in thickness; it is therefore reasonable to postulate that the layer comprises adsorbed alginate molecules, unlike the water response, where no clearly defined barrier layer is seen.

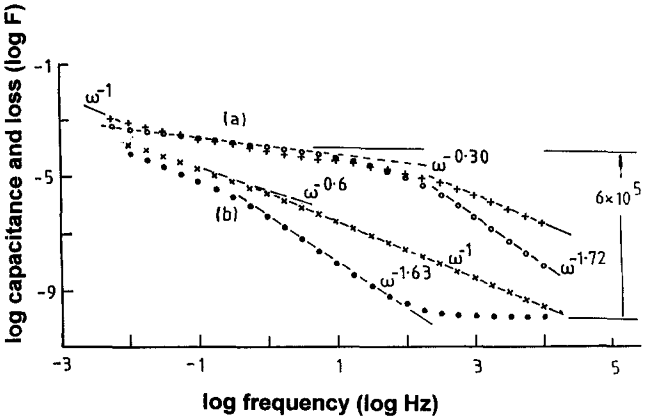

Fig. 2. Capacitance and dielectric loss for: (a) 1% sodium alginate solution; and (b) pure water. Alginate data: ○ and +, capacitance and loss. Water data: ● and x, capacitance and loss. Reproduced from [15] with permission.

The loss slope in the high frequency region for both the alginate solution and the water is approximately $-1$, indicating that $G$ is frequency independent, as one would expect for a d.c. transport process in an aqueous solution. It is also interesting to note that the sum of the low and high frequency capacitances is $-2.02$, which is close to the predicted value of $-2$. The responses of a range of alginate concentrations are shown in Fig. 3. At the lowest concentration shown (0.0082%), the response is similar to that seen for water but indicates a more well-defined barrier region, while at the highest concentration shown (5%) the response of the barrier region dominates the spectrum, with the d.c. conductivity process only seen at the highest frequencies studied. It was interesting to note that the bulk response increased linearly with alginate concentration, despite non-linear increases in viscosity being observed.

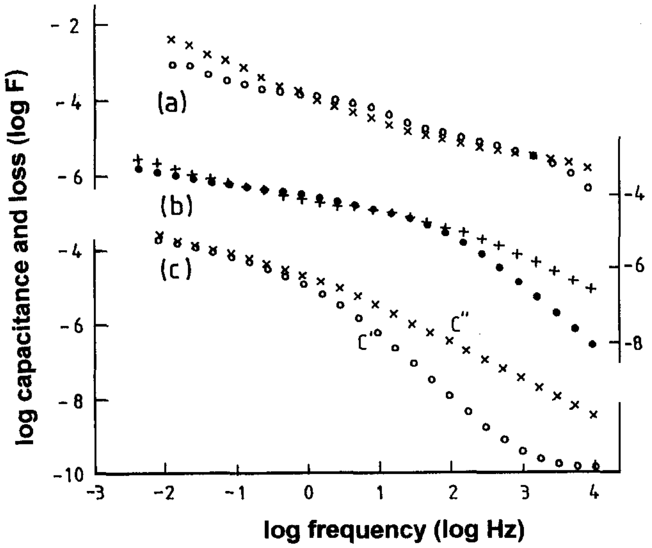

Fig. 3. Dielectric responses of three sodium alginate concentrations: (a) 5; (b) 1© 0.0082% w/v. Reproduced from [15] with permission.

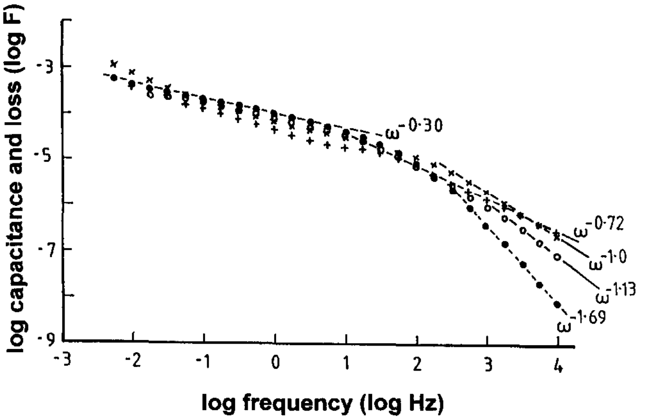

Fig. 4. Dielectric response of 1% sodium alginate containing 0.1% diclofenac sodium. 1% alginate data: ○ and +, capacitance and loss. Systems containing sodium diclofenac: ● and x, capacitance and loss. Reproduced from [15] with permission.

Similarly, the addition of calcium ions caused only a modest increase in the dielectric response, while a substantial increase in viscosity was observed. The chelating properties of calcium are well known, with the divalent cations forming an 'egg-box' structure between adjacent guluronic acid blocks [16]. These observations suggest that while the rheological behaviour of the system is a function of the polymer network, the dielectric behaviour reflects the movement of ions or other charges through the system.

The dielectric response of systems containing 0.1% of a model drug, diclofenac sodium, was also studied (Fig. 4). The addition of a comparatively small quantity of the drug had a marked effect on the dielectric response, not so much in terms of absolute values but in terms of the shape of the response curve. In particular, the high frequency conductance became frequency dependent, with $G \propto \omega^{0.28}$. This indicates that charge is no longer moving freely through the system but is instead moving between specific sites in the gel, i.e. a charge hopping, rather than a d.c. transport process is in operation. This response is compatible with the presence of an interaction between the drug and the gel network itself. While the exact mechanisms involved are not yet clear, the ability to detect such interactions has potentially considerable practical implications for understanding drug release processes.

These early studies therefore provided some basic indications as to the potential applicability of the low frequency dielectric technique to the study of gel systems. In particular, the ability to simultaneously monitor both the low (barrier) and high (bulk) frequency responses and the potential for studying drug-gel interactions provided the basis for further studies using other bioadhesive gel systems. The use of the technique in conjunction with rheological studies is also of interest, with the results presented above indicating that rheology gives information regarding the polymer network structure, while dielectric analysis yields information on charge movement through that system.

### 2.2. Dielectric analysis of poly(acrylic acid) (PAA) systems

#### 2.2.1. Structural characteristics of PAA hydrogels

The polymers of acrylic acid are the most widely used materials in the bio(muco)adhesion field, both in terms of fundamental research into bioadhesive mechanisms [17] and in the development of practical formulations [18]. They are long-chain, high-molecular weight, lightly cross-linked anionic macromolecules with a large number of COOH groups along the polymer backbone, thereby fulfilling the important structural requirements for good mucoadhesives [19].

A wide range of PAA polymers are on the market, including homopolymers cross-linked with allylsucrose or allylpentaerythritol (carbomers), homopolymers cross-linked with divinyl glycol (polycarbophils) and some copolymers. The best known representative of the carbomer group is Carbopol 934 (and its purified version, Carbopol 934P, intended for oral and mucoadhesive applications). Noveon AA-1 is the main representative of the polycarbophil group, having a tetra-functional cross-linker divinyl glycol, as opposite to the two-functional ones in carbomers.

In the dry state, the resin molecules are highly coiled and tightly packed. When placed in water, PAA polymers behave as anionic electrolytes, i.e. dissociate and partially uncoil due to the repulsion of negative charges generated along the polymer chains. The subsequent swelling is caused and determined by the difference in osmotic pressure inside the vicinity of the polymer chain clusters and the bulk medium. In the presence of a neutralising agent, the processes of ionisation, uncoiling and hydration are enhanced, leading eventually to the formation of a stable three-dimensional polymer network. It is a usual procedure, therefore, to neutralise PAA resins when including them in the formulation of semisolid dosage forms. However, when used in a non-hydrated ('dry') dosage form, PAA polymers swell at the site of application to form an acidic hydrogel. It is therefore of interest to study the properties of both neutralised and unneutralised PAA systems.

#### 2.2.2. The dielectric response of Carbopol 934

Initial studies on the dielectric response of polyacrylic acid gels focused on Carbopol 934 [20], which has been widely studied as a potential bioadhesive. Fig. 5 compares the response of 5% w/v gels with and without added neutralising agent (8% triethanolamine). The response again corresponds to the model proposed by Hill and Pickup [12], with a high frequency bulk process dominated by a d.c. conductance process and a lower frequency barrier layer. The addition of neutralising agent, which resulted in a marked increase in the rheological storage and loss moduli, caused an increase in the high frequency bulk response, although the low frequency barrier response remained largely unchanged.

The effects of adding 5 and 15% propylene glycol as a plasticiser and rheology modifier were also investigated. Fig. 6 shows the rheological response of the various systems. Both the storage and loss moduli increased on addition of the propylene glycol. While the former showing a trend with propylene glycol concentration, the rank order of the loss moduli for the 5 and 15% propylene glycol systems was frequency dependent. The tan $\delta$ values also increased on adding propylene glycol, indicating an increase in the viscous, as opposed to elastic behaviour of these gels. The dielectric behaviour is shown in Fig. 7, with both the high and low frequency responses being altered. The low frequency capacitance slope is more negative on addition of propylene glycol, indicating that the barrier layer has become less effective at blocking charge.

The effects of adding a model drug, chlorhexidine gluconate, at a concentration of 0.1% is shown in Fig. 8. Clearly, the presence of the drug has a profound effect on the dielectric response, more so than the addition of considerably greater quantities of triethanolamine. In particular, the barrier layer has become considerably less well-defined, indicating a more 'leaky' structure, i.e. the gel structure is becoming more open. Examination of the corresponding rheological data (Fig. 9) indicates that at low frequencies, the presence of the drug has a marked effect on the viscoelastic response, with a considerable increase in the tan $\delta$ values caused by both a decrease in $G'$ and an

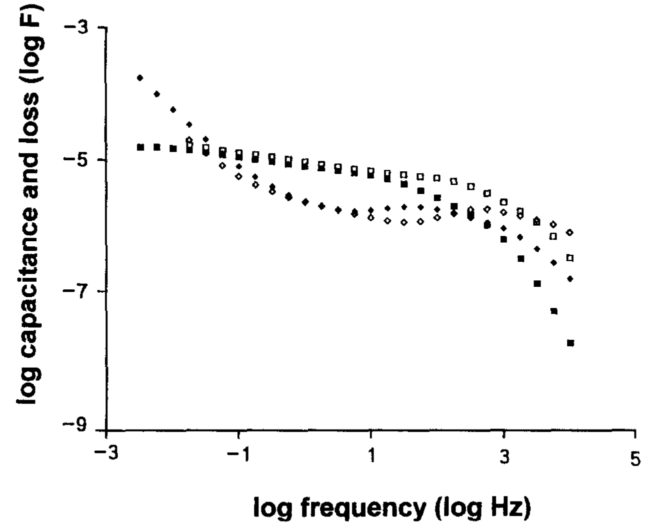

Fig. 5. Effect of the addition of triethanolamine on the dielectric response of Carbopol 934. ■, ◆: $C$, $G/\omega$ 5% Carbopol 934. □, ◇: $C$, $G/\omega$ 5% Carbopol 934 (8% TEA). Reproduced from [20] with permission.

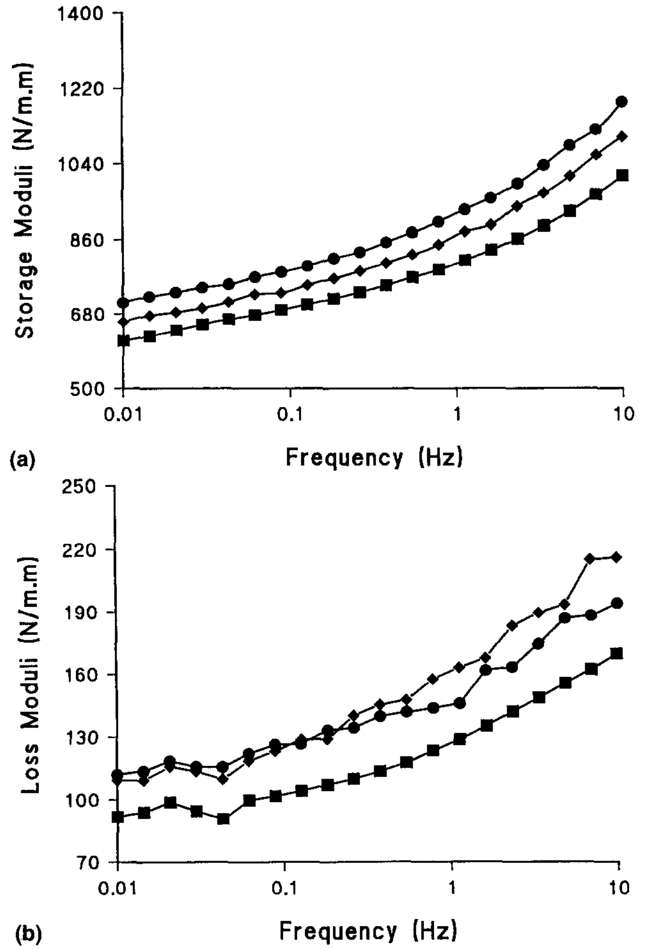

Fig. 6. Effect of propylene glycol on: (a), the storage modulus; and (b), the loss modulus of neutralised Carbopol 934. ■ 2.5% Carbopol 934, ◆ 2.5% Carbopol 934 with 5% propylene glycol, ● 2.5% Carbopol 934 with 15% propylene glycol. Reproduced from [20] with permission.

increase in $G''$. Taken together, these data suggest that the chlorhexidine gluconate is altering the gel structure, despite the low concentrations used. These findings have implications for understanding the mechanisms and kinetics of drug release from these systems.

Further studies [21] involved the examination of the effects of changing the neutralising agent on the structure and performance of a range of polyacrylic acids, namely Carbopol 934P, 974P, Noveon AA-1 and Carbopol EX-214. Carbopol 974P is a toxicologically preferred alternative to the widely used Carbopol 934P, while Noveon AA-1 (polycarbophil) is an insoluble, water-swellable PAA polymer. Carbopol EX-214 is the sodium salt of Carbopol 974P, hence in theory the gels formed should be equivalent to sodium hydroxide neutralised Carbopol 974P gels. The effects of changing the neutralising agent on these gels was studied using sodium hydroxide, triethanolamine (TEA) and tromethamine (Tris).

The effects of changing the neutralising agents on the dielectric response of Carbopol 974P is shown in Fig. 10, with Carbopol EX-214 included for comparison. A number of trends may be seen from these data sets. For example, the unneutralised gels show lower high frequency conductance values than do the neutralised systems for the reasons described earlier. TEA neutralised gels showed a greater low frequency conductance for all the polymers studied, indicating an increased accumulation of charge in the barrier (gel) layer present at the electrodes compared with the other agents. Examination of the high frequency conductance values, however, indicates no such trend. It may therefore be suggested that the charges present in TEA neutralised systems are more closely associated with the gel structure than with other neutralising agents. When compared with rheological measurements, the TEA systems were found to have higher $G'$ and lower tan $\delta$ values, i.e. the gels were more elastic, which is consistent with a greater degree of polymer chain extension. There may therefore be an association between the charge distribution anomalies detected by the dielectric analysis and the chain conformation, which in turn influences the rheological properties.

Examination of the rheological tan $\delta$ response of these systems and the force of detachment from a mucin surface also show differences, depending on both the choice of polymer and neutralising agent. The studies show Carbopol 974P and 934P to yield similar detachment values, with Noveon AA-1 and Carbopol EX-214 showing weaker bioadhesive properties under the experimental conditions used. However, while the differences between the neutralising agents are not as great, certain trends may be observed. In particular, the sodium hydroxide gels yield higher tan $\delta$ values and lower detachment forces. Indeed, there appeared to be an inverse association between these two parameters, at least within single data sets.

The effects of storage were then examined; neutralised and unneutralised gels were sealed in airtight plastic containers, protected from light and stored at room temperature (25 ± 3°C) for 6 months [22]. The storage and loss moduli showed marked changes over the storage period, with the $G'$ values decreasing substantially (Table 1), although smaller changes were seen for the rheological tan $\delta$ values due to the proportionate decrease in $G'$ and $G''$. Comparatively little is known regarding ageing effects in these systems, although likely mechanisms include chain scission or physical alterations in gel structure. Examination of the rheological data shows a number of trends. The tan $\delta$ values remained similar for the TEA and Tris neutralised systems, while a decrease in this parameter was seen for the sodium neutralised gels. Similarly, the detachment forces for the sodium systems showed an increase, while the values for the other neutralised

Table 1
Detachment forces and rheological tan $\delta$ values for fresh and aged poly(acrylic acid) systems

| Sample and neutralising agent | $G/\omega$ at $10^4$ Hz ($10^{-7}$ F) (fresh sample) | $G/\omega$ at $10^4$ Hz ($10^{-7}$ F) (aged sample) | Detachment force (mg) (fresh sample) | Detachment force (mg) (aged sample) | Rheological tan $\delta$ at 0.5456 Hz (fresh sample) | Rheological tan $\delta$ at 0.5456 Hz (aged sample) |
|---|---|---|---|---|---|---|
| Carbopol 934P | | | | | | |
| NaOH | 7.430 ± 0.365 | 8.670 ± 0.339 | 3973.3 ± 300.5 | 4340.8 ± 143.0 | 0.1336 ± 0.0003 | 0.1068 ± 0.0018 |
| TEA | 5.888 ± 0.361 | 6.598 ± 0.325 | 4276.9 ± 410.2 | 4200.1 ± 251.7 | 0.1252 ± 0.0010 | 0.1283 ± 0.0029 |
| TRIS | 4.875 ± 0.230 | 5.885 ± 0.220 | 4290.1 ± 342.0 | 4220.5 ± 602.2 | 0.1287 ± 0.0011 | 0.1296 ± 0.0019 |
| Unneutr. | 1.213 ± 0.090 | 1.384 ± 0.029 | 1126.7 ± 51.1 | 1290.9 ± 24.8 | 12.180 ± 0.552$^{a}$ | 7.162 ± 0.5098$^{a}$ |
| Carbopol 974P | | | | | | |
| NaOH | 6.501 ± 0.395 | 7.621 ± 0.215 | 4093.5 ± 149.9 | 4368.1 ± 217.7 | 0.2003 ± 0.0121 | 0.1547 ± 0.0001 |
| TEA | 5.623 ± 0.291 | 6.855 ± 0.198 | 4288.7 ± 265.8 | 4300.4 ± 320.5 | 0.1595 ± 0.0009 | 0.1600 ± 0.0095 |
| TRIS | 3.589 ± 0.185 | 4.159 ± 0.152 | 4226.4 ± 148.9 | 4406.8 ± 400.9 | 0.1781 ± 0.0228 | 0.1546 ± 0.0021 |
| Unneutr. | 1.108 ± 0.072 | 1.271 ± 0.056 | 1949.1 ± 92.3 | 1996.2 ± 81.6 | 3.677 ± 0.375$^{a}$ | 2.964 ± 0.274$^{a}$ |
| Noveon AA-1 | | | | | | |
| NaOH | 8.110 ± 0.550 | 10.690 ± 0.650 | 3113.0 ± 225.4 | 3251.7 ± 251.5 | 0.2863 ± 0.0447 | 0.2464 ± 0.0135 |
| TEA | 7.870 ± 0.352 | 11.270 ± 0.610 | 3237.2 ± 166.0 | 3184.4 ± 302.3 | 0.2365 ± 0.0051 | 0.2392 ± 0.0061 |
| TRIS | 6.808 ± 0.320 | 8.012 ± 0.391 | 3336.0 ± 182.9 | 3422.7 ± 149.5 | 0.2537 ± 0.0202 | 0.2756 ± 0.0177 |
| Unneutr. | 1.019 ± 0.065 | 1.211 ± 0.054 | 1935.7 ± 174.7 | 1970.8 ± 103.8 | 6.441 ± 1.134$^{a}$ | 2.857 ± 0.1091$^{a}$ |
| Carbopol EX-214 | 7.345 ± 0.291 | 9.441 ± 0.371 | 3290.8 ± 123.9 | 3644.1 ± 199.5 | 0.5172 ± 0.0370 | 0.5301 ± 0.0153 |

Adapted from [22].

[a] At frequency of 1.129 Hz.

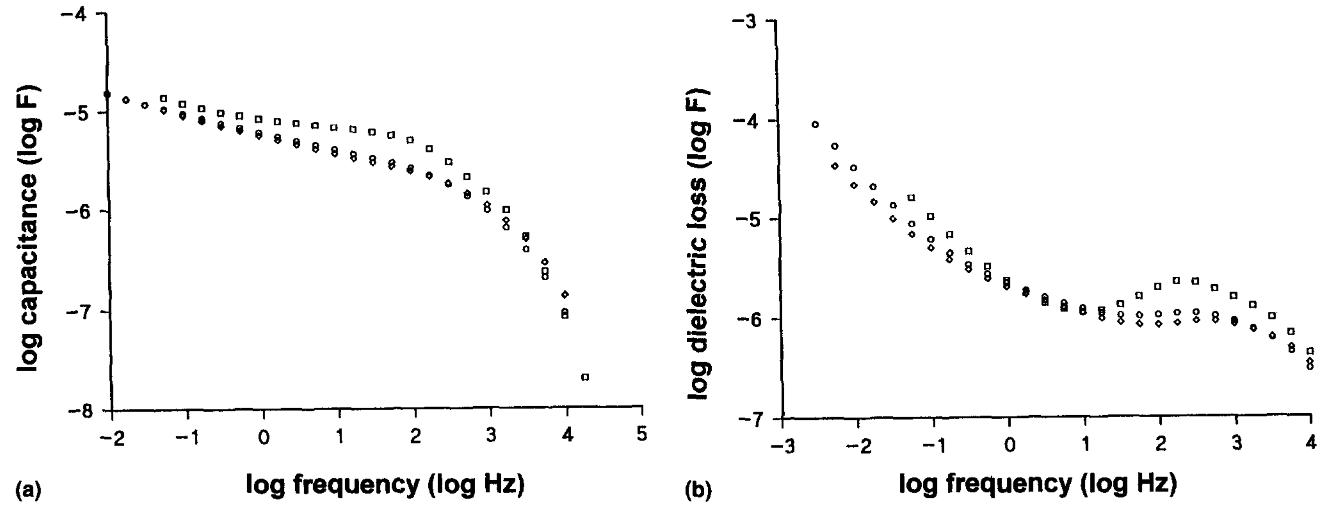

Fig. 7. Effect of propylene glycol on: (a), the capacitance; and (b), the dielectric loss of neutralised Carbopol 934. □ 2.5% Carbopol 934, ◇ 2.5% Carbopol 934 with 5% propylene glycol, ○ 2.5% Carbopol 934 with 15% propylene glycol. Reproduced from [20] with permission.

systems remained essentially constant. These results demonstrate a consistency in the observation of an inverse relationship between the tan $\delta$ values and the detachment force, suggesting a direct association between the viscoelastic properties of the gels and the force of detachment.

Examination of the dielectric data shows that the high frequency conductance increased on storage, although a similar universal trend was not observed for the low frequency response. However, a consistent decrease in dielectric loss at 0.1 Hz was seen for TEA neutralised systems (Fig. 11), suggesting a redistribution of charges may have taken place. While more work is required in order to clarify the association between changes in the dielectric response with changes in gel structure, these studies suggest that dielectric analysis may have a role in elucidating the mechanisms by which ageing processes take place in gels.

## 3. Conclusions

This review has outlined some of the ways in which dielectric analysis may be used in the study of bioadhesive gels. The use of this technique for the study of pharmaceutical systems is still in its infancy, hence over and above the objective of yielding information on the structure and behaviour of the gels, these studies were also intended as a means of examining the potential of the technique itself. The investigations described above have arguably been encouraging on both fronts, as the

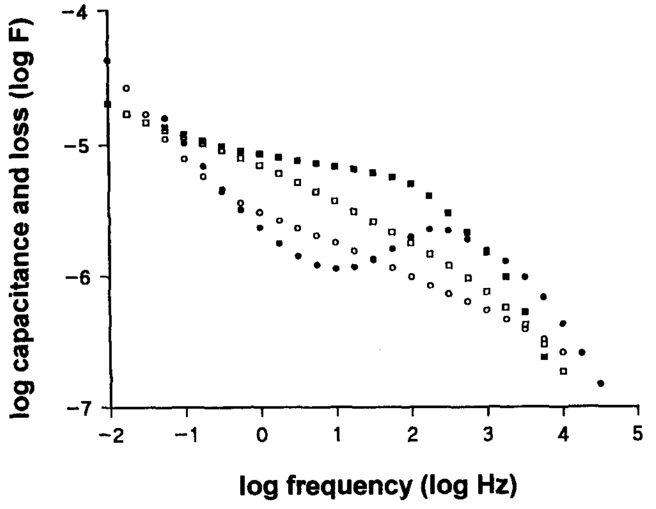

Fig. 8. Effect of chlorhexidine gluconate on the dielectric properties of neutralised 2.5% Carbopol 934. ■, ● $C$, $G/\omega$ Carbopol 934. □, ○: $C$, $G/\omega$ Carbopol 934 with 0.1% chlorhexidine gluconate. Reproduced from [20] with permission.

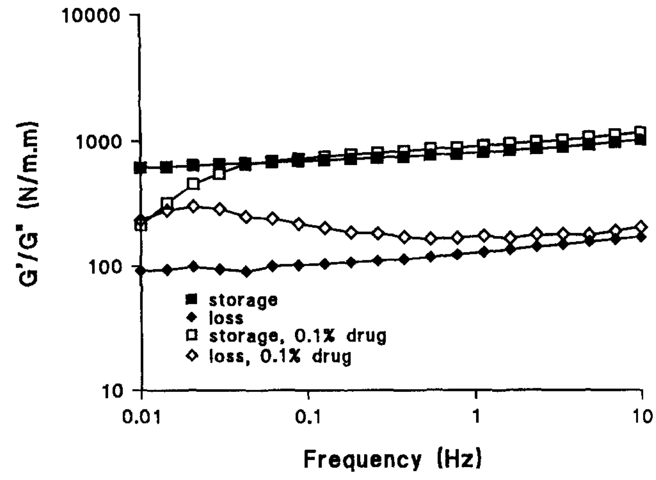

Fig. 9. Effect of chlorhexidine gluconate on the rheological properties of neutralised 2.5% Carbopol 934. ■, ◆ $G'$, $G''$ Carbopol 934. □, ◇: $G'$, $G''$ Carbopol 934 with 0.1% chlorhexidine gluconate. Reproduced from [20] with permission.

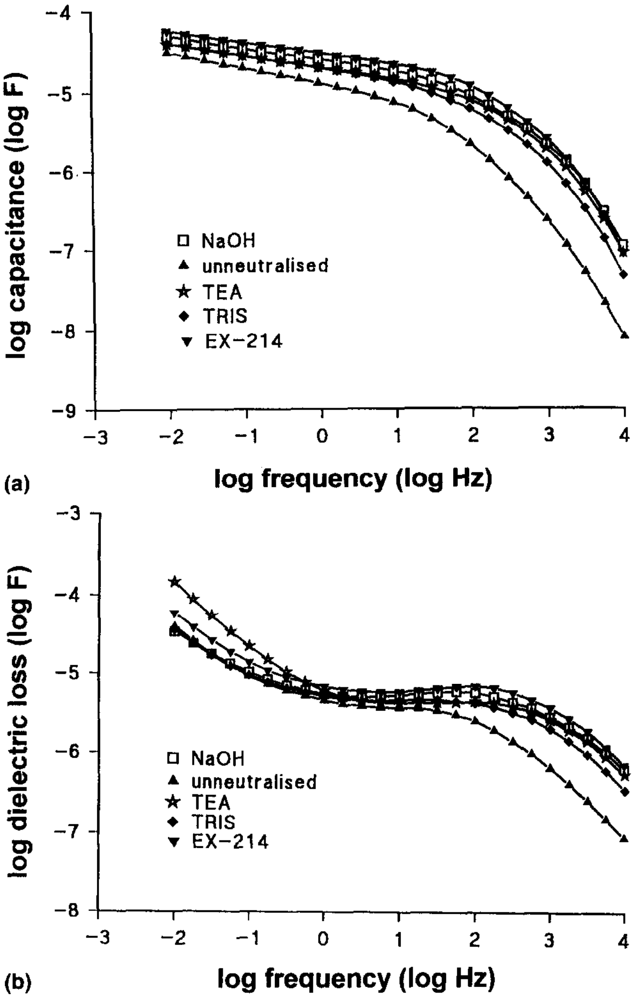

Fig. 10. Low frequency capacitance and (a) dielectric loss (b) of 2.5% Carbopol 974P gels with a range of bases in comparison to Carbopol EX-214. Reproduced from [21] with permission.

technique has given insights into, for example, the effects of added drugs, neutralising agents and storage effects on the gel system. Similarly, the technique is sensitive to certain changes in gel structure, particularly in terms of added drugs.

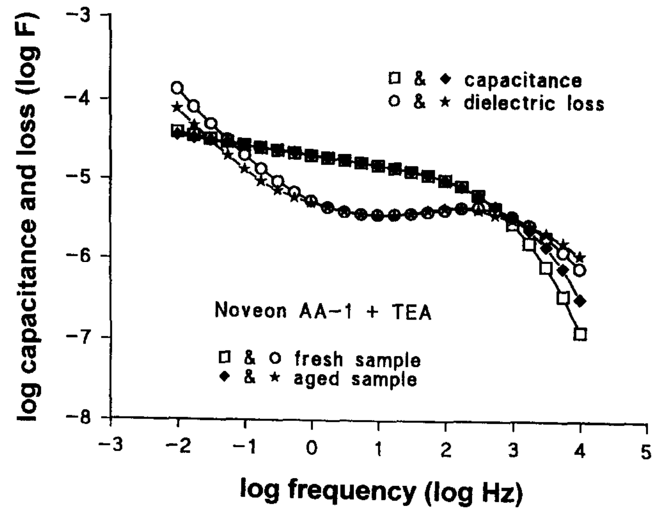

Fig. 11. Low frequency dielectric response of fresh (open symbols) and aged (solid symbols) 2.5% Noveon AA-1 gels neutralised with triethanolamine. Reproduced from [22] with permission.

It is perhaps useful to draw an analogy between the use of this technique and that of oscillatory rheology, which is reasonably well established within the bioadhesion field. Oscillatory rheology yields information on the relative elastic and viscous properties of gel systems, but as yet there has been limited success in modelling the frequency dependent response to specific structural features within the sample, at least within the pharmaceutical field. The ability to detect changes and rank various bioadhesive systems has, however, proved to be highly useful. With dielectric analysis, whereby an oscillating electric, rather than mechanical stimulus is applied, the modelling aspects of the approach are arguably at a more sophisticated stage, the disadvantage being that the applicability of knowing the electrical properties of a material is less immediately apparent than it is for rheological studies. By conducting studies such as those outlined here, we are building up a knowledge base of the types of system and phenomena for which dielectric analysis shows sensitivity, with a view to interpretation of the data in terms of specific structural features. Clearly, more work is required in order to fully explore the relationship between the dielectric response and the gel structure, but ongoing work continues to yield encouraging results. Procurement of more advanced dielectric equipment and curve fitting software has enabled us to place far greater emphasis on the modelling of the dielectric response, and it is this aspect of the work that is currently dominating our activities. It is therefore hoped that, with further study, dielectric analysis may become further established as useful tool for the study of pharmaceutical systems.

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