Moisture-Activated, Electrically Conducting Bioadhesive Hydrogels as Interfaces for Bioelectrodes: Effect of Formulation Factors on Cutaneous Adherence in Wet Environments

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SYNOPSIS

The effect of varying the composition of a polymer blend containing poly (methylvinyl ether-maleic anhydride) copolymer on the Brookfield viscosity of the blend and on the *in vitro* bioadhesive forces of resultant cast films was assessed. An increase in copolymer concentration increased both blend viscosity and film bioadhesion. Increasing the plasticizer concentration did not significantly alter bioadhesion but did influence film flexibility. Blend pH affected both viscosity and bioadhesion. However, for films to be biocompatible, formulation within the skin pH range was desirable. Films exhibited the ability to 'restick' after initial adherence, allowing repositioning of the adhered film *in vivo*. Factorial design experiments (2^2) showed that an additive bioadhesive effect occurred when copolymer and PVP concentrations were increased in the polymer blend. However, no interaction between copolymer and plasticizer was observed. Addition of sodium chloride to the polymer blend, necessary to render films electrically conducting for use as bioelectrode interfaces, decreased blend viscosity but did not exert a significant effect on film bioadhesion. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

The use of polymeric, electrically conducting gels as bioelectrode interfaces, although well established, is not without problems. The electrical resistance of such gels is dependent on a number of variables including composition, thickness, and the surface area of gel layer.[1] In addition, 'wet gels' leave messy residues and are difficult to reposition, often requiring further gel application. Adhesion of such gels is limited and usually requires incorporation of an additional pressure-sensitive adhesive disc.

The use of polymeric, electrically conducting, bioadhesive hydrogel films, cast onto Ag-AgCl inks screen printed onto suitable substrates, can enhance flexibility, conformability, and reduce residues. Because the hydrogel forms a tack-free adhesive film, there is no need for a gel retaining ring, suction, or disc of adhesive backing. A 'tail-piece' of conducting sensor extending beyond the gelled section can act as a means of connection to a monitoring device. This removes the need for bulky and heavy snap-fastener connectors.[1,2]

Many electrode sensor systems, including plate electrodes, 'Welsh-cup' suction types, and rigid retaining ring systems,[1] are inflexible and do not readily conform to body contours. Such designs have meant that the total system, complete with snap fasteners for connection to monitoring equipment, is bulky and heavy, thus exerting a considerable pull on the sensor. This has inevitably led to motion artefacts and, furthermore, the overall electrode size has often limited its clinical application.[3] A low-profile, conformable, light-weight, and relatively inexpensive bioadhesive sensor has, therefore, obvious

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advantages over previous designs. In addition, because the adhesive is moisture activated, it adheres to biological substrates under adverse conditions such as high humidity, where excessive perspiration can lead to the failure of conventional pressure-sensitive adhesive bonds, or when the biological substrate is immersed in water or a physiological fluid, for example, in the noninvasive monitoring of fetal heart rate.

In the present study, moisture-activated bioadhesive films derived from a copolymer of methyl vinyl ether and maleic anhydride, are evaluated for their adhesion *in vitro* to neonate porcine skin. The effect of formulation variables on adhesion have been considered in detail, with the use of factorial design experiments to highlight interactions between formulation components.

EXPERIMENTAL

Materials

Polyvinylpyrrolidone (PVP, Kollidon™90, USP Grade) was obtained from BASF, Ludwigshafen, Germany. Gantrez AN-139, a copolymer of methyl vinyl ether and maleic anhydride (PMVE/MA), was provided by ISP. Co. Ltd., Manchester, UK. All other chemicals used were of analytical reagent quality.

Preparation of Bioadhesive Films

Aqueous polymer blends were variously prepared, as follows. The required weight of copolymer was added to water maintained between 95–100°C and the mixture stirred vigorously until a clear solution was formed. Glycerol, sodium chloride, sodium hydroxide, and PVP were added sequentially as required and the blend weight adjusted to its final value with water. Bioadhesive films were prepared by casting, to a defined thickness, the aqueous blends, using a conventional casting knife technique, onto a polyester-lined glass plate surrounded by a PVC barrier. The cast blends were then air dried for 24 h at ambient temperature to produce clear hydrogel films.

In vitro Adhesion Measurements

The adhesion of all films was quantitatively evaluated using a bioadhesion tester based on a linear variable displacement transformer (LVDT), designed and previously validated in our laboratory.[4] Full thickness, hairy porcine skin, thoroughly wetted by immersion in water for 10 s, was attached with cyanoacrylate adhesive to an upper pedestal linked to the LVDT via a sensor. The film (1 cm^2) was attached with double-sided adhesive tape to the lower, moveable platform that was driven by a stepping motor. During the test procedure, the platform was moved downwards at a predetermined rate controlled by the motor drive logic board. As movement occurred to the upper pedestal, this was detected by the output from the LVDT, which was recorded potentiometrically. The force generated was measured by a previously calibrated spring contained within the sensor housing.

Skin Model

Full-thickness neonate porcine skin was used as a model for human skin. Excess subcutaneous fat was removed, the skin samples washed in distilled water, placed between layers of aluminium foil, and stored at −18°C until required. Storage under these conditions was for a maximum of 4 months, although a number of reports suggest that freezing for up to 1 year has no significant effect on skin quality.[5,6]

Viscosity Measurements

All viscosity measurements were carried out using a Brookfield Syncho-lectric Viscometer, model LVT (Brookfield Engineering Laboratories, Inc., Stoughton, MA). All measurements were carried out in triplicate, using a standardized procedure, at room temperature using an appropriate spindle size.

RESULTS AND DISCUSSION

Porcine skin is a good model for human skin with regard to hair sparseness, presence of subcutaneous fat, epidermal proliferation, and both the orientation and distribution of blood vessels.[7,8] In order to develop an electrically conducting, bioadhesive film with strong cutaneous adherence in a wet environment, the porcine skin model was thoroughly hydrated before use and excess water was removed prior to the determination of adhesive strength. Films were thus applied in the dry state directly to the wet substrate and adhered immediately upon hydration.

Aqueous solutions containing various concentrations of PMVE/MA copolymer were prepared as described according to the manufacturer's instructions.[9] Figure 1 demonstrates that increasing the

copolymer concentration in the aqueous blend results in significant increases in the *in vitro* adhesion of the resultant films. In fact, for blends containing 10% w/w copolymer, the increase in adhesion of films was significant ($p < 0.001$) compared to copolymer concentrations of 6 and 8% w/w. This was true irrespective of the plasticizer (glycerol) content of the films.

It is necessary to include a plasticizer when using PMVE/MA because the glass transition temperature (T_g) of the copolymer is high, reportedly 151°C.[10] Hydrolysis of the PMVE/MA five-membered anhydride ring structure, which includes two carbon atoms in the polymer backbone and, therefore, confers rigidity on the system, to the free acid only reduces T_g by approximately 10°C due to the increased flexibility of the free acid structure.[10] Films formed from solutions of the free acid are, therefore, very brittle. However, glycerol may be added as a plasticizer to enhance film flexibility. It is apparent from Figure 1 that the plasticizer concentration does not significantly influence the bioadhesive properties of PMVE/MA films formed from pH 5 polymer blends ($p > 0.05$). However, it was also noted that in blends where the concentration of plasticizer exceeded the concentration of copolymer, films did not form properly. In such cases, it is apparent from Table I that there is a resultant decrease in film adhesiveness and that the effect is more pronounced at pH 2 because, at this pH, the viscosity of the polymer blend is reduced compared to pH 5.

Films cast from blends containing 10% w/w copolymer were capable of being 'restuck' after initial positioning (Fig. 2). Although adhesion is reduced with each subsequent 'restick,' this is, nevertheless, an important attribute for any topical adhesive if repositioning is required. The 'restick' capability of PMVE/MA bioadhesive films is, therefore, a distinct advantage over conventional, pressure-sensitive electrically conducting adhesive gels that require a further application prior to repositioning the sensor on the body surface.

Blends formulated from aqueous solutions of PMVE/MA plasticized with glycerol had a pH value of approximately 2. In addition to the potential for cutaneous irritancy, such formulations also have extremely low viscosities, as shown clearly in Figure 3. Increasing the pH of the solution by the addition of sodium hydroxide to the aqueous blend, thus forming the disodium salt of PMVE/MA, increased the Brookfield viscosity to a maximum value at about pH 5–6, above which pH the viscosities decreased quite rapidly (Fig. 3). For the particular application where PMVE/MA films are to be used as

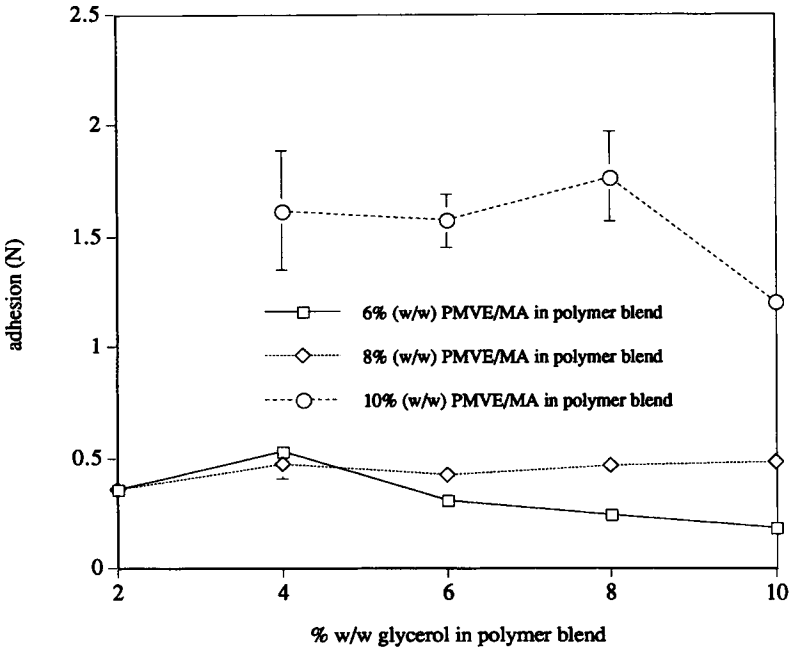

Figure 1 The effects of varying copolymer and plasticizer concentrations in the polymer blend (pH 5) on the *in vitro* bioadhesive forces to wet neonate porcine skin of the resultant films. Films cast from blends containing 10% w/w PMVE/MA and 2% w/w glycerol were too brittle to test for adhesiveness. Error bars represent standard deviations.

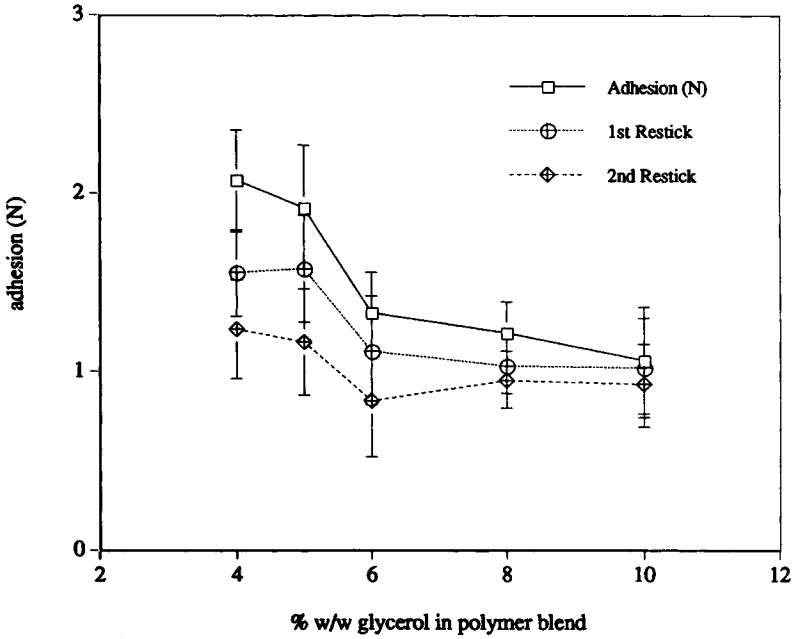

Figure 2 'Restick' capabilities, as determined *in vitro* by forces of bioadhesion to wet neonate porcine skin, of films formed from a polymer blend (pH 5) containing 10% w/w PMVE/MA and a varying plasticizer concentration. Error bars represent standard deviations.

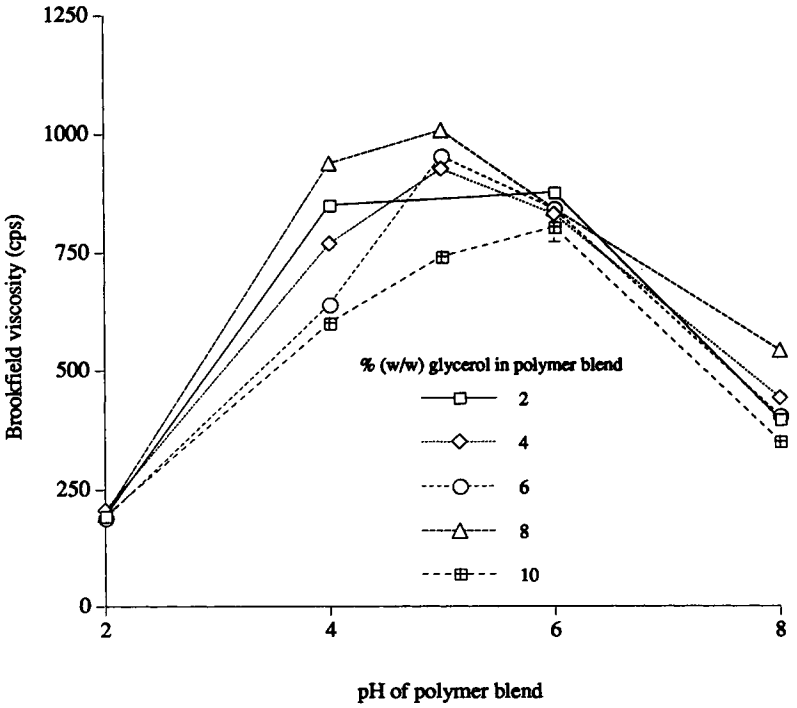

Figure 3 Variation in Brookfield viscosity (cps) of a polymer blend containing 10% w/w PMVE/MA with changes in pH and plasticizer concentration. Error bars represent standard deviations.

conducting, bioadhesive interfaces for noninvasive fetal heart rate monitors, the effect of pH is of some importance. Thus, because the pH of neonatal skin immediately after birth is reported to have a mean value of 6.34, with a range of 3.0 to 8.0,[11] blends formulated within this pH range are likely to be highly biocompatable. When the pH of the blend was not adjusted into the skin pH range, remaining typically around 2, PMVE/MA films exhibited consistently lower adhesive properties *in vitro* (Table I). This effect may have been due to the decreased blend viscosity, resulting in the formation of thinner films upon casting (Fig. 3).

The maximum viscosity upon pH increase, even for blends containing 10% w/w PMVE/MA, is very low, only approaching 1200 cps at pH values between 5 and 6. Films cast from very low viscosity blends tend to be extremely thin and are, therefore, difficult to handle during manufacturing.[12] For moisture-activated bioadhesive films that are water soluble, a thicker film is generally more desirable because it will be longer lasting in use. Addition of a thickening agent to the blend may enhance the viscosity and, therefore, enable the production of thicker films. Polyvinylpyrrolidone (PVP) is a well-known pharmaceutical thickening agent.[13] In addition, it possesses inherent adhesive properties and is highly soluble in water, an advantage in the formulation of a bioadhesive hydrogel. PVP is known to complex with PMVE/MA[9] and, when crosslinked, has significant protein-binding capability.[14] PVP, therefore, promotes water uptake, possesses intrinsic adhesivity, and improves film machinability. Addition of PVP to aqueous PMVE/MA blends significantly increased their viscosities (Fig. 4). This was particularly apparent when the concentration of PMVE/MA was increased to 15% w/w (with 7.5% glycerol to keep an identical copolymer/plasticizer ratio). The resultant increase in viscosity, compared to a blend containing no PVP, was approximately of three orders of magnitude. In fact, a gel containing 15% w/w PMVE/MA and 9% w/w PVP was more viscous than the maximum value measurable by the Brookfield viscometer, i.e., greater than 2×10^6 cps. The effect of PVP on the *in vitro* adhesion properties of films is also shown in Figure 4. It is apparent that an increase in the copolymer concentration from 10 to 15% w/w increased the adhesion of films for all concentrations of PVP.

The detailed effects on film bioadhesive properties of varying both PMVE/MA and PVP blend concentrations is more difficult to assess from the data in Figure 4. However, by designing factorial experiments, the effects on subsequent film bioadhesion of individual blend components, as well as any additive effects between components, may be statistically assessed. Initially, a control study was required to compare the effects on film bioadhesion of increasing PMVE/MA concentration in the presence (5% w/w) and absence (0% w/w) of PVP (Table II). The Newman-Keuls multiple range test (Fig. 5) for the mean *in vitro* bioadhesion values listed in Table II, indicated that an increase in the PVP concentration of the blend, from 0% to 5% w/w with 10% w/w PMVE/MA, did not exert a statistically significant effect on the bioadhesion of films to wet, neonate porcine skin ($p > 0.05$). However, for blends containing 15% w/w PMVE/MA, increasing the

Table I Effect of Polymer Blend pH on the *in vitro* Adhesion Characteristics of Bioadhesive Films Containing PMVE/MA

% w/w PMVE/MA	% w/w Glycerol	pH	Mean Adhesion (N) + SD $n = 3$
6	4	2	0.279 ± 0.019
6	6	2	0.162 ± 0.045
6	8	2	0.165 ± 0.005
6	10	2	0.143 ± 0.041
6	2	5	0.361 ± 0.034
6	4	5	0.530 ± 0.049
6	6	5	0.311 ± 0.025
6	8	5	0.245 ± 0.045
6	10	5	0.182 ± 0.008
8	4	2	0.258 ± 0.109
8	6	2	0.179 ± 0.093
8	8	2	0.255 ± 0.017
8	10	2	0.176 ± 0.053
8	2	5	0.355 ± 0.050
8	4	5	0.470 ± 0.066
8	6	5	0.426 ± 0.25
8	8	5	0.464 ± 0.033
8	10	5	0.481 ± 0.022
10	4	2	1.575 ± 0.232
10	6	2	1.061 ± 0.230
10	8	2	0.873 ± 0.016
10	10	2	0.633 ± 0.009
10	4	5	1.616 ± 0.269
10	6	5	1.570 ± 0.122
10	8	5	1.766 ± 0.204
10	10	5	1.197 ± 0.049

Note: Films cast from all blends containing 2% w/w glycerol at pH 2, and those cast from blends at pH 5 containing 10% copolymer and 2% glycerol, were too brittle to test for adhesiveness.

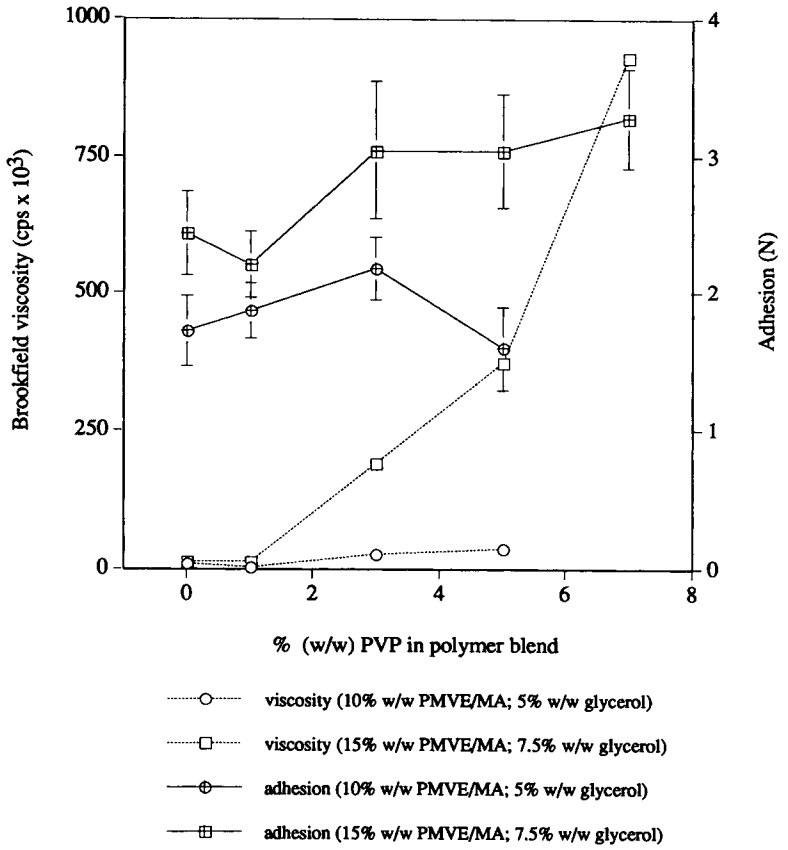

Figure 4 Brookfield viscosities of two polymer blends (pH5, 10 and 15% w/w PMVE/MA, respectively) containing varying amounts of polyvinylpyrrolidone (PVP) and the *in vitro* forces of bioadhesion to wet neonate porcine skin of the resultant films. The ratio of PMVE/MA to plasticiser was kept constant. Error bars represent standard deviations.

PVP concentration from 0% w/w to 5% w/w did significantly increase the *in vitro* bioadhesive characteristics of the resultant films ($p < 0.05$). In addition, bioadhesion of films cast from blends containing 10% w/w PMVE/MA, compared to 15% w/w PMVE/MA, was significantly reduced (Fig. 5). From Figure 4, it is apparent that, for blends containing 10% w/w PMVE/MA, the effect of adding PVP to the formulation increased the force of bioadhesion up to a maximum at 3% w/w PVP. A Newman-Keuls multiple range comparison (Fig. 5) of the mean adhesion values obtained for films cast from blends containing 10% w/w PMVE/MA, confirms that addition of 3% w/w PVP to the blend significantly enhanced ($p < 0.05$) the *in vitro* bioadhesive properties of films cast from this blend as compared to those with no PVP present.

To investigate if changes in bioadhesive properties due to increasing blend concentrations of both PMVE/MA and PVP were due to an additive effect, a 2^2 factorial experiment was designed. This design allows the investigation of two components of a given study at two levels to see if any interactive effects have occurred. In this case, the components were PMVE/MA and PVP and the levels were two different concentrations (1% w/w and 5% w/w PVP; 10% w/w and 15% w/w PMVE/MA) for each component. Bioadhesion data (Table II) from this study was statistically analyzed by two-way ANOVA with repeated measures (Table III). From this analysis it is apparent that an increase in the copolymer concentration of the blend, from 10% w/w to 15% w/w, significantly increased the mean *in vitro* bioadhesion forces for the films ($p < 0.001$). An increase in the PVP concentration of the blend, from 1% w/w to 5% w/w, also significantly enhanced *in vitro* film bioadhesion. The combination of an increase in both the copolymer and PVP concentrations in the blends was shown to exert a significant effect on the *in vitro* bioadhesion of the resultant films.

From Table I, an increase in the PMVE/MA concentration of the blend from 10 to 15% w/w only

Table II Effect of Polymer Blend on *in vitro* Adhesion of Bioadhesive Films to Neonate Porcine Skin in the Presence of Polyvinylpyrrolidone (PVP)

Polymer Blend (% w/w)	Adhesion (N) ± SD $n = 6$
10% PMVE/MA, 0% PVP, 5% glycerol	1.725 ± 0.257
10% PMVE/MA, 1% PVP, 5% glycerol	1.866 ± 0.199
10% PMVE/MA, 5% PVP, 5% glycerol	1.597 ± 0.303
10% PMVE/MA, 5% PVP, 7.5% glycerol	1.903 ± 0.421
10% PMVE/MA, 3% PVP, 5% glycerol	2.179 ± 0.225
15% PMVE/MA, 1% PVP, 7.5% glycerol	2.210 ± 0.241
15% PMVE/MA, 5% PVP, 7.5% glycerol	3.035 ± 0.415
15% PMVE/MA, 0% PVP, 7.5% glycerol	2.430 ± 0.305
15% PMVE/MA, 3% PVP, 7.5% glycerol	3.040 ± 0.497
15% PMVE/MA, 5% PVP, 5% glycerol	3.011 ± 0.494

appeared to exert a significant increase on film bioadhesion in the presence of 5% w/w PVP. It is also apparent from the bioadhesion data in Table II that an increase in the PVP blend concentration from 1 to 5% w/w did not exert a dramatic effect on the bioadhesion of films cast from blends containing 10% w/w PMVE/MA. However, when the copolymer concentration was increased to 15% w/w, a significant increase in adhesion was observed when the

Table III ANOVA (Two-way with Repeated Measures) of the Effect of Co-polymer (PMVE/MA) Concentration on *in vitro* Bioadhesion to Neonate Porcine Skin in the Presence of 1% and 5% w/w PVP (2^2 Factorial Design)

Source	*df*	*SS*	MS	*F*-Value	*p*
PMVE/MA	1	4.7615	4.7615	52.38	< 0.001
PVP	1	0.4676	0.4676	5.14	0.035
Interaction	1	1.7876	1.7876	19.67	< 0.001
Error	20	1.8188	0.0909		
Total	23	8.8355			

df = degrees of freedom; *SS* = sum of squares; MS = mean square error; *p* = significance probability.

PVP concentration of the blend was increased from 1 to 5% w/w. ANOVA (Table III) for this data indicates that the effects on film bioadhesion observed due to increasing, respectively, PMVE/MA blend concentration from 10 to 15% and PVP blend concentration from 1 to 5%, were influenced by an additive effect between the two components. This effect may have been due to a direct physical interaction between the copolymer and PVP or it may be an indirect effect due to the increased viscosity of the gel (Fig. 4), resulting in a higher concentration of PMVE/MA and PVP being present in a given cast film.

The effects of glycerol on viscosity and *in vitro* bioadhesion in blends containing 15% w/w PMVE/MA and 5% w/w PVP were also investigated. Although the viscosity appears to decrease with increasing plasticizer concentrations (Fig. 6), this effect was relatively small. Gels containing 14% w/w glycerol have a viscosity of around 2.7×10^5 cps. The blend concentration of plasticizer, as expected,

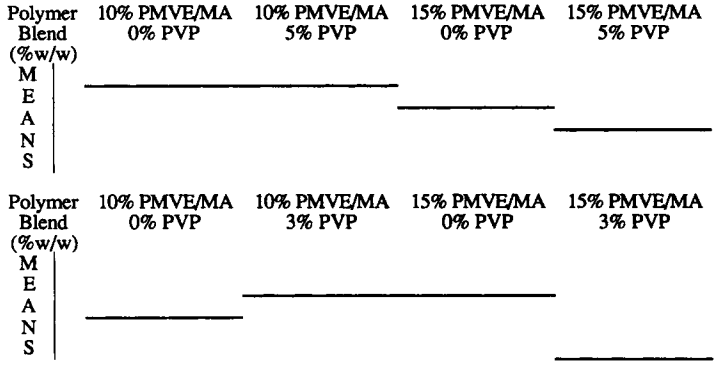

Figure 5 Graphical representation of the Newman-Keuls multiple comparisons test. At the 0.05 significance level, the mean *in vitro* forces of bioadhesion to wet neonate porcine skin of any two groups underscored by the same line were not significantly different.

did not appear to exert any significant influence on the bioadhesion of films (Fig. 6).

To investigate the possibility of an additive effect between plasticizer and PMVE/MA, a 2^2 factorial experiment was designed to compare the effect of 10% and 15% w/w PMVE/MA blend concentrations on film bioadhesion in the presence of 5% and 7.5% w/w glycerol. In this case, it was not possible to carry out a control study where the effect of PMVA/MA in the presence and absence of glycerol would be assessed, because the plasticizer must be present to ensure adequate film flexibility. The film bioadhesion data (Table II) was again analyzed by a two-way ANOVA with repeated measures, indicating (Table IV) that, although increasing PMVE/MA concentration in the blend from 10 to 15% w/w did result in a significant increase in film bioadhesion ($p < 0.001$), increasing the glycerol concentration from 5 to 7.5% w/w did not significantly affect this property ($p = 0.29$). There was no statistically significant additive effect between the components.

The effect on film bioadhesion of increasing the PMVE/MA concentration in the blend from 10 to 15% w/w in the presence of 5% glycerol and 7.5% w/w glycerol is apparent from Table II. For both concentrations of glycerol, the effect of increasing the blend copolymer concentration from 10% to 15% w/w resulted in a dramatic increase in film adhesion that was statistically significant ($p < 0.001$, Table IV). However, ANOVA (Table IV) demonstrates that the glycerol concentration of the blend did not exert any significant effect on film bioadhesion. Thus, adjusting the glycerol concentration of the blend appears only to influence the flexibility of the films formed. This is probably also the case for glycerol concentrations higher than 7.5% w/w because, from Figure 6, film bioadhesion did not appear to be dramatically influenced by glycerol concentrations in the blend of up to 14% w/w.

Hydrophilic hydrogels may be rendered electrically conducting by including salts such as sodium

Table IV ANOVA (Two-Way with Repeated Measures) of the Effect of Copolymer (PMVE/MA) Concentration on *in vitro* Bioadhesion to Neonate Porcine Skin in the Presence of 5% and 7.5% w/w Glycerol (2^2 Factorial Design)

Source	*df*	*SS*	MS	*F*-Value	*p*
PMVE/MA	1	10.2848	10.2848	49.78	< 0.001
glycerol	1	0.2446	0.2446	1.18	0.290
Interaction	1	0.0654	0.0654	0.32	0.580
Error	20	4.1310	0.2066		
Total	23	14.7258			

df = degrees of freedom; *SS* = sum of squares; MS = mean square error; *p* = significance probability.

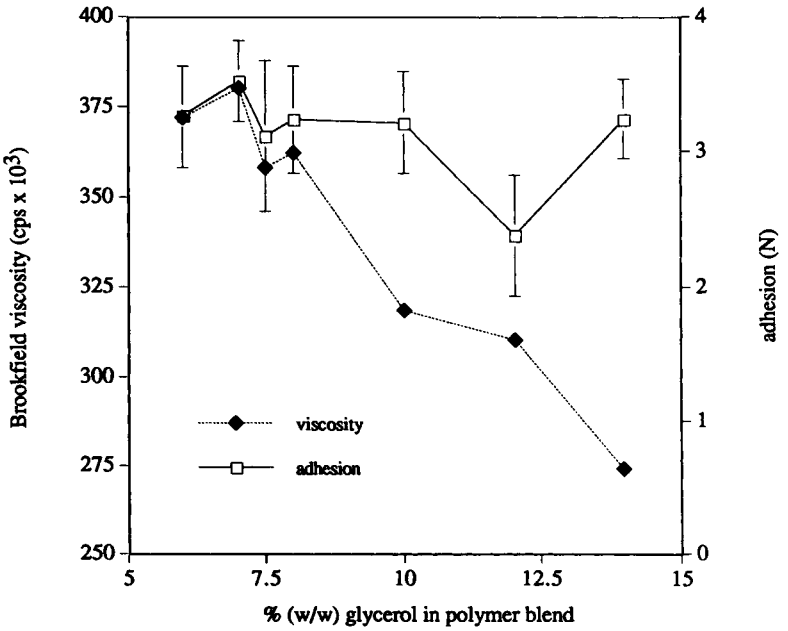

Figure 6 The effect of varying the plasticizer concentration of a polymer blend (pH 5) containing 15% w/w PMVE/MA on the Brookfield viscosities of the blends and on the *in vitro* forces of bioadhesion to wet neonate porcine skin of the resultant films. Error bars represent standard deviations.

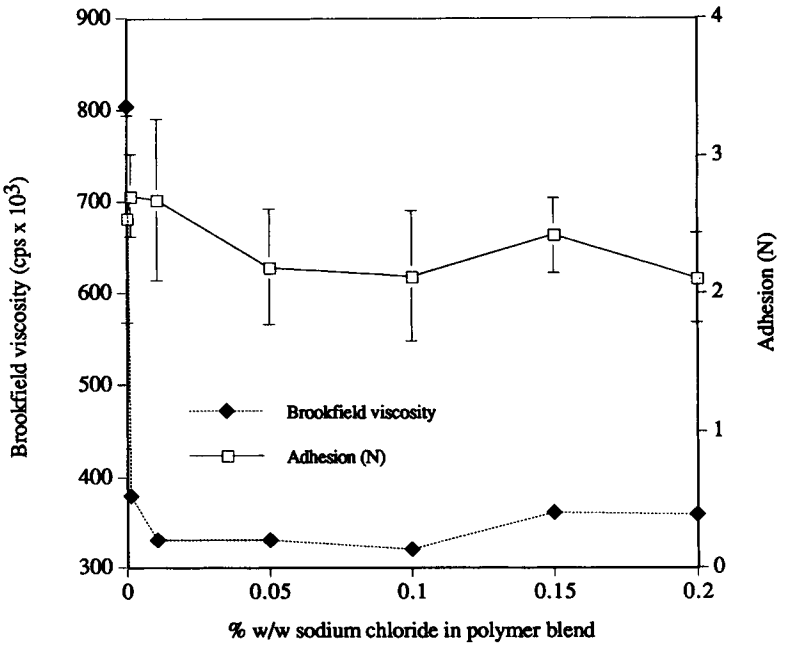

Figure 7 The effect of varying the sodium chloride concentration of a polymer blend containing 15% w/w PMVE/MA and 7.5% w/w plasticiser on the Brookfield viscosities of the blends and on the *in vitro* forces of bioadhesion to wet neonate porcine skin of the resultant films. All blends were pH 5. Error bars represent standard deviations.

or potassium chloride in the aqueous polymer blend.[1] Thus, in this study sodium chloride was added to a blend of PMVE/MA (15% w/w), PVP (5% w/w), and glycerol (7.5% w/w) in order to enhance the electrical conductivity of the resultant cast film. From Figure 7 it is apparent that the presence of salt dramatically decreased the viscosity of the blend, though this effect does not seem to be concentration related. The presence of salt does not exert any significant effect ($p = 0.13$) on the adhesion characteristics of the bioadhesive film within the range tested (Fig. 7). This is a particularly useful characteristic because security of adhesion will be of prime importance in the application of such systems as interfaces for bioelectrodes operating in wet environments.

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