SKIN ADHESIVE HYDROGELS FOR BIOMEDICAL APPLICATIONS

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SUMMARY

Skin adhesive hydrogels (water-swollen polymer gels) have been used for many applications such as drug delivery devices, wound dressings and electrical interfaces for various medical devices. This thesis presents an investigation of compositional factors that affect skin adhesion. The three properties that dictate skin adhesive behaviour of a material are its ability to absorb additional water, the availability of lipophilic groups at the skin surface and an appropriate balance of compliance and cohesion in the rheological behaviour of the gel.

Hydrogels based on sodium 2-acrylamido 2-2methylpropane sulfonic acid (NaAMPS) and the sulphopropyl ester of acrylic acid (SPA) showed good potential to produce adhesive gels. NaAMPS produced the most cohesive gel and this is due to the interaction of the amide group on one chain with the sulphonate group on another. SPA gels alone were insufficiently cohesive (in the absence of other monomers) due to the lack of an amide group, and left residue on the skin surface. As a result, the gels containing SPA appeared to be more adhesive than NaAMPS gels.

The addition of acrylic acid to the gels reduced surface residues and enhanced cohesion, due to increased intermolecular forces within the gel. The peel strength of the gel was improved, perhaps in part by removal of interfacial water. Acrylic acid was also shown to enhance the behaviour of the gel by modification of its dynamic-mechanical properties. Acrylamide and N-iso-propyl acrylamide were not as effective as acrylic acid in increasing peel strength. The addition of poly(ethylene-co-vinyl-acetate) (DM 137) improved adhesion by increasing the hydrophobic components at the surface of the gel, which in turn interacted with the lipids in the skin. The surface activity of DM 137 was shown by a reduction in the polar component of the surface energy of the gel. When both DM 137 and acrylic acid were incorporated into the gel, peel and cohesive strength increased further and the effects of the two components were complementary, supporting the evidence that the components were acting at different locations.

Future work should include investigating the incorporation of acrylamide and N-iso-propyl acrylamide into SPA and NaAMPS:SPA based gels, since the acrylamide and the N-isopropyl acrylamide would provide amide groups to the system which are not present in SPA. Supplementing the structure of SPA with amide groups would be expected to enhance the cohesive properties of SPA gels sufficiently to be practical for use as a skin adhesive.

Keywords: hydrogel, polymer, bioadhesive, skin-adhesive, poly (ethylene glycol) dimethacrylate, pressure-sensitive adhesives

To my family

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LIST OF ABBREVIATIONS

DM137	Poly(ethylene-co-vinyl-acetate)
DSC	Differential Scanning Calorimetery
DVS	Dynamic Vapour Sorption
EWC	Equilibrium Water Content
G'	Elastic modulus
G''	Viscous modulus
HPMC	Hydroxypropyl methylcellulose
IPN	Interpenetrating Polymer Network
M bis A	Methylene bis Acrylamide
NaAMPS	Sodium 2-acrylamido 2-2methylpropane sulfonic acid
NaOH	Sodium hydroxide
NIPA	N-Iso-Propyl acrylamide
PBH	Propyl 4-hydroxybenzoate
PEG	Polyethylene glycol
PEGDM	Polyethylene glycol dimethacrylate
PI	Photoinitiator
PSA	Pressure Sensitive Adhesive
Rad	Radian
RH	Relative humidity
SPA	Sulphopropyl ester of acrylic acid (K salt)
SPE	Sulphopropyl ammonium betain of ethyl methacrylic acid
SPI	Sulphopropyl ester of itaconic acid (K salt)
SPM	Sulphopropyl ester of methacrylic acid (K salt)
SPP	N,N-Dimethyl-N-methacrylamido-propyl-N-(3-sulphopropyl) ammonium betaine
SPV	1-(3-Sulphopropyl)-2-vinyl pyridinium -betaine
S.E.M.	Scanning Electron Microscopy
T. Strength	Tensile Strength
UV	Ultra Violet
XL	Cross-linker
$\delta\upsilon$	Deformation
Tan δ	Dampening factor, G''/G'
ϕ_2	Swelling factor

Chapter 1
Introduction

1.1 Introduction to Hydrogels

Hydrogels are polymeric materials that exhibit the ability to swell but not dissolve in water or a biological fluid, and retain a significant fraction of water within their structures. The biocompatibility of hydrogels is attributed to the presence of this water and the unique surface properties that it conveys. It is the low interfacial tension, high permeability to small molecules and soft rubbery nature which gives hydrogels the potential to act as a biomaterial[1]. This potential was exploited by Wichterle and Lim when they reported in 1960, the capabilities of hydrogels fabricated from cross-linked poly (2-hydroxyethyl methacrylate)[2].

Hydrogels, from a physical and mechanical point of view, are similar to soft biological tissues[3]. This has enabled hydrogels to be used for numerous biomedical applications which includes soft contact lenses, synthetic articular cartilage, membranes for reverse osmosis and kidney dialysis, drug delivery systems, wound dressings and biosensors.

Hydrogel polymers are made by either thermal polymerisation or photopolymerisation. Thermal polymerisation requires a monomer solution containing a thermal initiator, typically azo-bis-isobutyronitrile to be cured in an oven at 60 degrees Celsius for three days followed by a post cure at 90 degrees Celsius for three hours[4]. Photoinitiation requires a monomer solution containing a photoinitiator such as Irgacure 184, to be exposed to light of the appropriate wavelength for the photoinitiator used.

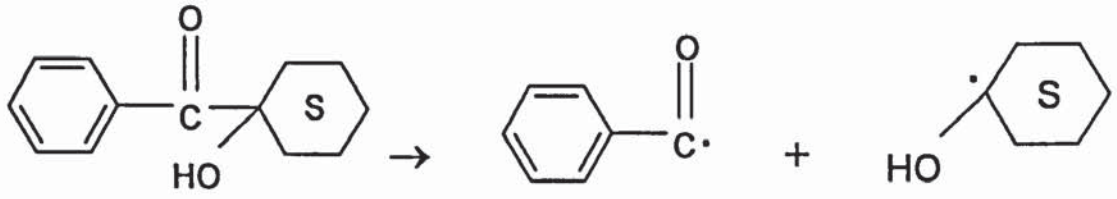
1.2 Photopolymerisation

Photopolymerisation is the utilisation of light energy for polymerisation and is the basis of UV curing. This process requires that light is absorbed by the system and is utilised to effect the formation of new chemical bonds. Photopolymerisation requires the utilisation of photoinitiators and photo cross-linkable monomers[5]. As UV light energy is emitted, it is absorbed by the photoinitiator in the liquid, causing it to fragment into reactive species. These species are free radicals which react with the unsaturated compounds in the liquid, causing them to polymerise rapidly.

The free radical class of initiators represents greater than 90% of the commercially used initiators for polymers of vinyl and methacrylate monomers, unlike cationic curing, which is more limited in application. Irgacure 184, an alpha cleavage initiator, was used in this thesis for preparing hydrogels as it is highly efficient, has non-yellowing properties and produces relatively low odour. Alpha cleavage initiators are efficient because they generate free radicals by a unique unimolecular process, of light absorption, to generate radicals. These initiators are typically differentiated by their absorption profiles. Irgacure 184 has an absorption peak of 240-250 and 235-330 nm.

The light source used for UV curing is of the arc type. Arc type light includes the medium pressure mercury lamp which is currently the overwhelming choice for UV polymerisation due to its high power (200-700 Watts/inch) and principal emission lines which are absorbed by most commercially available photoinitiators such as Irgacure 184. The emission spectra of the lamp must overlap the absorption spectra of the chosen initiator to enable UV curing to occur[6].

UV curing has a great number of advantages over thermal curing such as rapid network formation (seconds), reduced energy expenditure and lower solvent emissions thereby reducing air pollution[5].



Irgacure 184 $h\nu\rightarrow$ 2 reactive species

Figure 1.1 Irgacure 184 generating free radicals by light absorption.

1.3 Equilibrium Water Content (EWC)

Cross-linked hydrophilic polymers swell when placed in water (or a biological fluid) until an equilibrium is reached. The water that is absorbed by a hydrogel network can be

quantitatively represented by the equilibrium water content, EWC, which is the ratio of the weight of water in the hydrogel to the weight of the hydrogel at equilibrium hydration, expressed as a percentage by the following equation:[7].

$$EWC = \frac{[(\text{Wet weight}) - (\text{Dry weight})]}{(\text{Wet weight})} \times 100\ \%$$

Equation 1.1

The EWC is the most important single property of a hydrogel. It dictates all the fundamental properties of the hydrogel including mechanical properties, surface properties, permeability and biological interactions. The EWC is determined by the nature of the monomer and cross-linker used, cross-link density, temperature, pH, and tonicity. The biocompatibility of a hydrogel is to a large extent determined by the state and volume of water in the matrix. The water acts as to plasticize hydrogels just as it does in soft tissue, thus enabling hydrogels to exhibit similar physical properties.

1.4 Water Structuring in Hydrogels

There is a great deal of evidence to suggest that water in polymers can exist in more than one state and that the states of water can affect the properties of the polymer. The imbibed water in hydrogel membranes are frequently characterised by the terms freezing and non-freezing water. These can be obtained by analysis of the melting endotherms obtained by differential scanning calorimetery (DSC), where the water that is strongly associated with polar groups in the polymer matrix is unable to freeze and does not, therefore, contribute to the melting endotherm. In this way the relative proportions of freezing and non-freezing water in the polymer can be determined.

Non-freezing water is considered to be water that directly hydrogen bonds with polar groups or which strongly interacts with the ionic residues of the polymer matrix. While the freezing water does not interact with the polymer matrix it often occupies large pores, showing a level of hydrogen bonding characteristic of pure water. However, the true nature of water present in a polymer network is probably one of a continuum of states

between the two extremes. The properties of a hydrogel are strongly influenced both by the EWC of the hydrogel and by the ratio of freezing to non-freezing water[8,9,10].

Non-freezing water (bound water)		Freezing water (free water)
Bound	Intermediate	Free
Primary bound	Secondary bound	
Tightly bound	Interfacial	Bulk

Table 1.1 Comparison of the terms used in water binding studies.

1.5 Differential Scanning Calorimetery

In 1964 Perkin-Elmer developed the differential scanning calorimetery technique which allows the ratio of freezing to non-freezing water to be calculated[10]. Differential scanning calorimetery (DSC) requires energy input to maintain both the sample and the reference holder at the same temperature. This energy is recorded. When an endothermic transitions occurs the energy input to the sample is increased, while for exothermic transitions the energy input into the reference holder is increased. When a transition occurs a peak is displayed and the energy input to the sample or reference holder is measured directly as the area under the peak. The heat of fusion for water associated with polymers is the same as that for pure water. Therefore the amount of freezing water and subsequently non freezing water for a polymer sample can be determined.

1.6 Mechanical Testing

Most hydrogels in their hydrated state have low mechanical strength in comparison to their non-water swollen state and are prone to dehydration. Therefore, it is difficult to determine their mechanical properties in absolute terms. However, standard test conditions and specimen geometry for use with the Hounsfield Tensiometer, established by Trevett and Tighe[11], provide adequate conditions that give useful results for comparative information.

1.7 Contact Angle Measurements

Contact angle measurements enable the surface free energy of a hydrogel to be determined. The total surface free energy is made up of polar and dispersive components. A skin adhesive with a high polar component will adhere best to wet skin whereas an adhesive with a high dispersive component will adhere better to greasy skin. This is important when considering the application of skin adhesive hydrogels.

Contact angles are obtained via the resolution of the forces at the liquid-vapour interface, the solid-liquid interface and the solid-vapour interface. The three phase interface is formed by a drop of liquid, usually diiodomethane or water on a solid surface, with the hydrogel in air.

In 1805, Young[12] derived an equation to determine the forces at the point of contact of a sessile drop of liquid on a solid surface as shown in figure 1.1

$$\gamma sv = \gamma sl + \gamma lv \cos \theta \qquad \text{Equation 1.2}$$

In 1869, Dupre[13] concluded that the reversible work of adhesion of a liquid and a solid (Wa), could be expressed as:

$$Wa = \gamma s + \gamma lv - \gamma sl \qquad \text{Equation 1.3}$$

The two equations are combined to give the Young - Dupre equation.

$$Wa = (\gamma s + gsv) + \gamma lv (1 + \cos \theta) \qquad \text{Equation 1.4}$$

where

γlv = liquid-vapour interfacial free energy

γsl = solid-liquid interfacial free energy

γsv = solid-vapour interfacial free energy

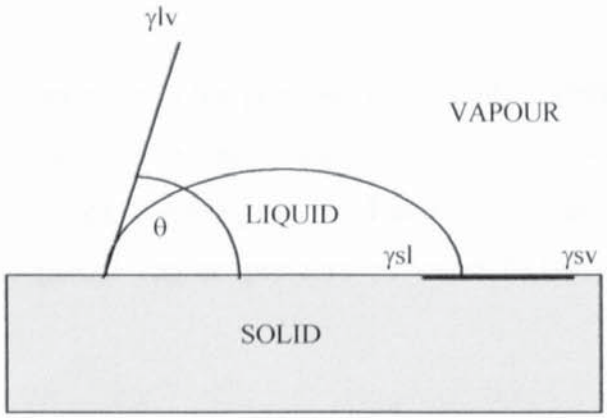


Figure 1.2 Individual components of the solid surface free energy.

Owens and Wendt[14] resolved the polar and dispersive forces to give the surface energy of a dehydrated polymer. The expression is shown below.

$$1 + \cos\theta = (2/\gamma lv)\ \{\ (\gamma lv^{d}\ \gamma s^{d})^{0.5} + (\gamma lv^{p}\ \gamma s^{p})^{0.5}\ \} \qquad \text{Equation 1.5}$$

This equation relates the contact angle to the polar and dispersive forces of the solid. Therefore, if the polar and dispersive components for two wetting solutions are known, the polar and dispersive components for the solid can be derived by the solution of simultaneous equations. Additionally, the total free surface energy can be determined by adding the values of the polar and dispersive components.

$$\gamma s^{t} = \gamma s^{d} + \gamma s^{p} \qquad \text{Equation 1.6}$$

Diiodomethane and distilled water are frequently used as the wetting liquids[15] due to their high total surface free energies and their balance of polar and dispersive components, as shown in the table below.

Liquid	γs^{d} (mN/m)	γs^{p} (mN/m)	γs^{t} (mN/m)
Water	21.8	51.0	72.8
Diiodomethane	48.1	2.3	50.4

Table 1.2 Polar and dispersive components for water and diiodomethane.

1.8 Dynamic Vapour Sorption

Most materials are sensitive to the presence of moisture. They may retain water by bulk absorption, surface absorption, capillary condensation, chemical reaction, formation of a solution or a combination of these process. The moisture content of a material is directly dependent on the partial vapour pressure of water (relative humidity) in the sample environment.

The DVS operates by recording the sample mass over time and by varying the relative humidity of air, thus enabling a broad range of physiochemical aspects of moisture behaviour to be studied. These include equilibrium moisture content, rates of drying and sorption, heats of sorption and de-sorption, kinetics of moisture uptake and loss, and hysteresis due to sorption/de-sorption cycling. The rate of moisture uptake or loss is particularly important for skin adhesive hydrogels which may be stored for long periods of time, as variation in their water content may change their adhesive properties[16].

1.9 Dynamic Mechanical Properties

The dynamic-mechanical properties of a hydrogel can be measured using a rheometer. The adhesive is placed between parallel plates and subjected to dynamic torsion or compression. The resulting moduli and viscosity values are measured as a function of the oscillation frequency. Either constant stress or strain can be used in these measurements[16].

The moduli can be divided into in phase (G') and out-of-phase (G") components and plotted as a function of frequency (ω). The spectrum produced is fairly sensitive to minor changes in molecular weight, degree of cure and copolymer composition.

The dynamic-mechanical properties, mainly G' as a function of frequency, have been correlated to tack and peel. The rationale for the correlation can be briefly described as follows: Peel adhesion or tack can be thought of as a combination of two processes: (1) the bonding process, which occurs at relatively long times or small frequencies and (2)

the de-bonding process, which occurs at relatively short times or high frequencies. The moduli is measured at low and high frequencies and should be able to be related to measured tack and peel. For the bonding process a low G' is required at low frequencies and the de-bonding process requires a high G' at a higher frequency, as both of these would lead to high tack and/or peel. The higher the slope of a G' versus ω plot, the better the adhesive properties[16,17].

Skin adhesives have unique rheological properties. The adhesive should ideally be easily deformed in a fraction of a second. Dahlquist found the 1 second compliance of a typical pressure-sensitive adhesive which has good probe tack to be 10^{-6} $cm^2/dyne$[18].

1.9.1 Simple Deformation Under an Applied Constant Force (Hookean Response)

A cube of material, assuming it behaves as an ideal solid, that has a constant 'pushing' force applied to it will obey Hooke's Law of elastic deformation and will deform to a new position.

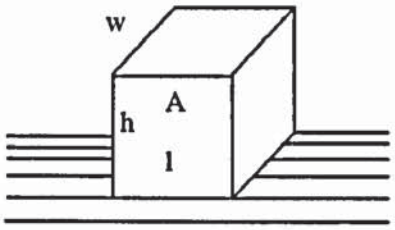


Figure 1.3 A cube of material (e.g. hydrogel) with its base fixed to a surface.

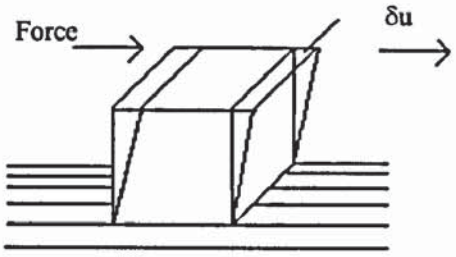


Figure 1.4 A cube with a constant 'pushing' force being applied to the upper part of the cube.

This type of deformation with the base fixed and the upper moving is known as shear deformation. The deformation δu and height h are used to define the shear strain as:

$$\text{Shear Strain} = \delta u/h \qquad \text{Equation 1.7}$$

The shear strain is simply a ratio of two lengths and has no units, it enables the measurement of pre-defined deformations without having to specify the size of sample. The Shear Stress is defined as:

$$\text{Shear Stress} = F/A \qquad \text{Equation 1.8}$$

Where F is the force of pushing and A is the area of the upper cube length x width. The units of Shear Stress are N/m^2. For a purely elastic material Hooke's law states that stress is proportional to the strain:

$$\text{Stress} = G \times \text{Strain} \qquad \text{Equation 1.9}$$

Where G is defined as the Shear Modulus, a constant. Thus doubling the stress would double the strain consequently the material is behaving with a linear response. If the stress is removed and the strain returns to zero then the material has undergone a fully recoverable deformation and no flow has occurred.

1.9.2 Simple Flow Under an Applied Constant Shear Stress (Newtonian Response)

If we assume that the cube behaves as an ideal fluid, when we apply the shear stress (force) the material will deform as before but in this case the deformation will continually increase at a constant rate, with increasing force.

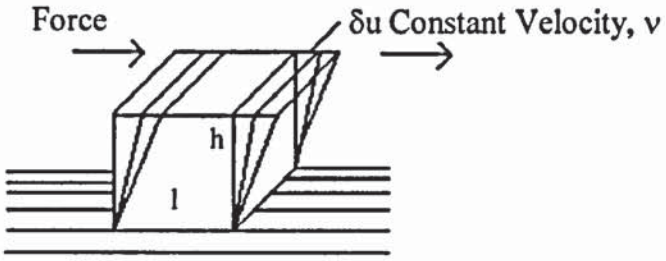


Figure 1.5 A cube under a constant shear stress.

$$\gamma = \delta u \times 1/h \times S \qquad \text{Equation 1.10}$$

The rate of change of strain is referred to as the shear strain rate (shear rate) and is found by the rate of change with regards to strain as a function of time i.e. the differential δ. σhear strain/δ.time. The shear rate obtained from an applied shear stress will be dependent upon the material's resistance to flow i.e. its viscosity. The units of viscosity are $Nm^{-2}S$ and are known as Pascal seconds (Pas). Since the flow resistance is equivalent to force/displacement, then it follows that:

$$\text{Viscosity} = \text{Shear Stress/ Shear Rate } (\eta = \sigma/\gamma) \qquad \text{Equation 1.11}$$

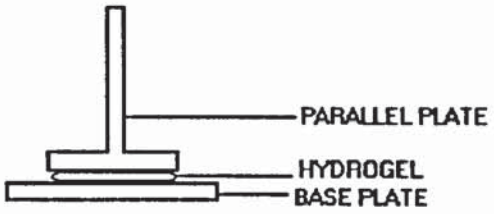


Figure 1.6 The parallel plate system used for testing the dynamic mechanical properties of a hydrogel.

1.10 Adhesive Properties

Tack is the adhesive property related to bond formation, and is the property which enables the adhesive to form a bond with the surface of a substrate upon brief contact

under light pressure. Tack is also the sensation experienced when an individual brings their finger lightly into contact with a pressure sensitive adhesive for a short time and then withdraws it. When the pressure or time in contact with the adhesive is varied, a variation in difficulty of withdrawing from the adhesive can be detected. Testing tack in this manner has the shortcomings of being subjective, non-quantifiable, uncertain in differentiation among adhesives except for tests made at the same time, and indicative only of skin bonding. Test for pressure-sensitive tack can be classified into three groups:

- rolling ball, rolling cylinder and rotating drum tests in which distance travelled, energy lost or force observed in the interaction of these objects with an adhesive is measured.

- probe tests in which the bottom tensile strength of the bond formed between the tip of a probe and the adhesive after a short time at low pressure is taken as the tack level.

- 90 or 180 degree peel tests involving low external contact pressure and short application time, in which the peel force is taken as the tack value.

1.10.1 Rolling Ball Tack Test

The rolling ball tack test is the oldest and most widely used mechanical test. The most common form of the rolling ball test involves a stainless steel ball 1.1 cm in diameter, released at a defined elevation on an inclined track so as to roll to the bottom onto the horizontal, upward-facing adhesive. The distance the ball travels along the adhesive gives an inverse measure of tack, the greater the distance travelled, the less tacky the adhesive. Gillespie investigated the rolling ball test further and discovered instances where the ball slowed down as it was acted upon by a constant force whilst on the adhesive and lost energy in proportion to the distance travelled. He also found that heavy, dense balls tended to lose energy in proportion to time, opposite to light balls which lose energy in proportion to distance[18].

1.10.2 Probe Tack Test

Probe tack tests are mechanical simulations of finger tack tests. The tip of the probe is briefly brought into contact with an adhesive under low contact pressure and then pulled away at a fixed rate, during which the peak force of separation is measured. Probe tack tests can examine separately each of the factors involved in adhesive bond formation, pressure, contact time, temperature, composition of probe and rate of separation.

1.10.3 Peel Testing

Peel adhesion is a measure of how difficult it is to remove the adhesive following attachment to an adherend. If an adhesive is to adhere to an adherend one fundamental requirement must be satisfied, that is, the measured surface energy of the adhesive must be equal to or less than that of the adherend. Peel adhesion testing, again, has many variables such as contact pressure and time against the substrate, the angle of peel and the withdrawal speed. Peel indicates ease of removal and cohesive failure is easily detected in a peel adhesion test[16].

1.10.3.1 The 180 Degree Peel Test

This vertical peel test consists of a fixed solid surface on which an adhesive is adhered. The adhesive is subsequently peeled from the solid surface by a grip directly above the end of the adhesive. The adhesive is peeled from bottom to top, bending back on itself as the peeling occurs. The peeling occurs at 500mm/min using 100N load. The grip of an adapted Hounsfield Tensiometer is interfaced to a computer which determines the peel strength in N/mm.

1.10.3.2 The 90 Degree Peel Test

The perpendicular peel test consists of a two wooden platforms, a base to support the plate and the plate which slides over the base. This plate enables the arm or substrate to remain in position whilst sliding over the base, allowing the angle of peel to remain

constant. This ensures the adhesive leaves the adherend directly below the peel grip. The adhesive is subsequently peeled from a material, for example skin, by a grip directly above the end of the adhesive at 500mm/min using 100N load. As in the 180 degree peel test, the grip of the Hounsfield Tensiometer relates the information to a computer which determines the peel strength in N/mm.

1.11 Interpenetrating Polymer Networks (IPNs)

The poor mechanical strength of hydrogels in which large amounts of water are absorbed limits their application. This can be controlled by morphological changes in the form of interpenetrating polymer networks (IPNs). IPNs have been defined as a combination of two polymers, each in network form, at least one of which has been synthesised and/or cross-linked in the presence of the other. Only if there is "total mutual solubility" then full intermolecular interpenetration occurs. Since this is seldom the case, some phase separation usually occurs but this may be reduced by chain entanglement between the polymers. The main beneficial effects relate to mechanical behaviour as well as water binding, surface and optical properties. IPNs produce materials that are stiffer and stronger but less elastic than hydrogel copolymers of similar water content[7,19].

Hydrogels are versatile materials since they can be rendered more or less hydrophilic by copolymerisation of multiple monomers of different hydrophilicities. Most hydrogels for biomedical applications have inhomogenities (clustering) and phase separation structures that can affect both the diffusion and mechanical properties of the hydrogel. These properties are adjustable by modifying the degree of cross-linking, branching copolymerisation and swelling (hydration).

The composite hydrogels are useful in tailoring desired properties from different polymers into a single hydrogel. This range of properties enables hydrogels to be used for a variety of biomedical applications[20].

1.12 Hydrophilic Polymers

There are many types of hydrophilic polymers and they include ampholytic, anionic, cationic, non-ionic and zwitterionic polymers. The polyampholytes and zwitterionic polymers have the potential to swell more in salt than in pure water[21]. Zwitterionic monomers are macromolecules in which an internal salt has been incorporated in the side chain[22]. An example of a zwitterionic monomer includes N,N-dimethyl-N-methacryloyloxyethyl-N-(3-sulphopropyl) ammonium betain (SPE)[23].

Zwitterionic monomers can be used to form ampholytic polymers, a class of highly dipolar polymeric materials showing a wide spectrum of unique and specific properties[24]. The properties of ampholytic polymeric materials include hydrophilicity, good biocompatability, moderately high mechanical strength in the water-swollen state, and adjustable permeability to liquids depending on the type of fixed-charge groups present and the conditions of polymer preparation.

Linear ampholytic polymers with a balanced stoichiometry are known to be water-soluble only in the presence of low-molecular-weight salt; chain expansion increases in salt solutions of high concentration. The behaviour of stoichiometricaly balanced ampholytic polymers in aqueous salt solution has been referred to as antipolyelectrolyte behaviour (Fig.1.6)[25]. This behaviour for ampholytic hydrogels is characterised by increasing water content in response to rising ionic strength in the external solution, in contrast to polyelectrolyte behaviour where ionised hydrogels are characterised by increasing water content in response to declining ionic strength. Antipolyelectrolyte swelling behaviour has been observed near a net fixed-charge density of zero, while polyelectrolyte behaviour has been observed when the net fixed-charge deviates from zero[26].

The experiments of Huglin and Rego[22] with hydrogels containing SPE and ethylene glycol dimethacrylate showed that the sulphobetainic character of SPE enhances the water uptake capacity of the hydrophobic methacrylic chain. The increase is not especially pronounced owing to the incorporation of methylene groups along side the sulphonate and ammonium moieties. As the temperature increases from 278 to 303K,

the volume fraction of polymer within a hydrogel decreases from 0.412 to 0.338 ϕ_2. However, from 303 to 343K a constant value of $0.338\phi_2$ is obtained. Furthermore, the gels change from opaque (278-293K) to transparent (293-343K). With the decrease in swelling, there is an increase in mechanical properties, indicating that the water is not plasticising the gel but is in fact improving its mechanical properties[24]. It is the swelling ability of these gels which enable them to be manipulated to become skin adhesive.

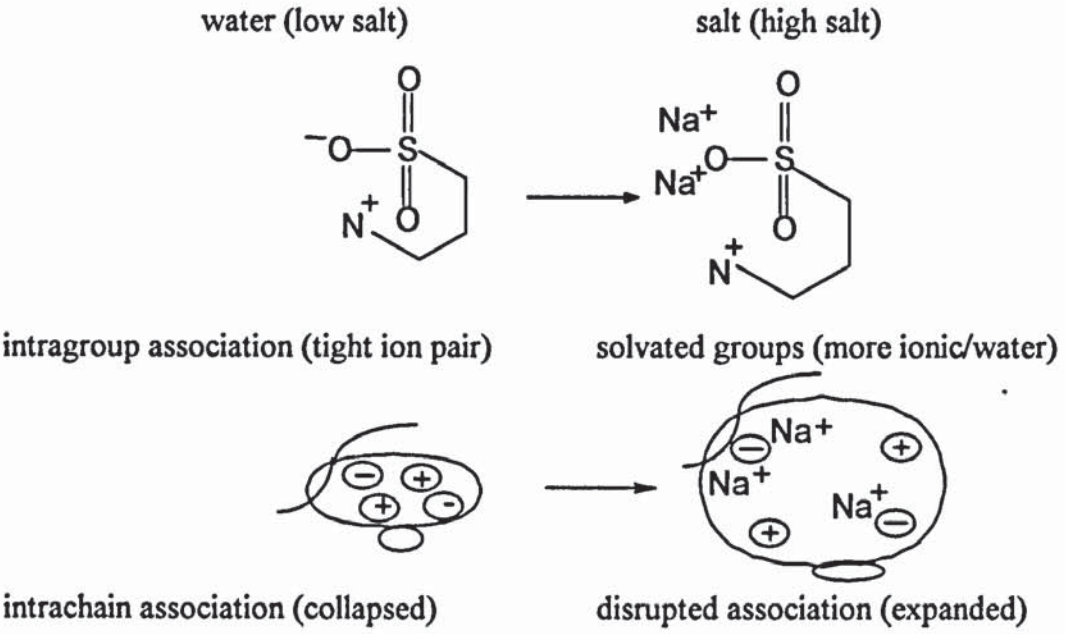


Figure 1.7 The ampholyelectrolyte swelling behaviour for a zwitterion (betaine) polymer.

1.13 Skin Adhesive Hydrogels

Skin adhesive hydrogels have many biomedical applications, they include transdermal drug delivery systems, biosensors and wound dressings. They must possess a high EWC but only be partially hydrated to increase the gel's affinity for water. A low interfacial surface tension is required for the gel to adhere to the skin and polar external groups are favoured for maximum interaction with the skin lipids. The water content and the control of hydrodynamics is critical for bioadhesion. Therefore the role of the polymer structure in controlling water binding is an essential element in the understanding and design of skin adhesive hydrogels.

Bioadhesive hydrogels must also have a high mechanical strength to enable the gels to remain cohesive should the gels require removal and repositioning on the body. This is often achieved by the addition of a water soluble interpenetrant polymer. Biosensors are required to be conductive and ionic monomers are often employed for this purpose, e.g., US patent 4,674,512[27].

1.13.1 Transdermal Drug Delivery

The skin has been used for decades as the site for topical administration of dermatological drugs to achieve localised pharmacological action in skin tissues. Recently, the potential of using skin as a site for systemic delivery of therapeutic drugs has been recognised[28].

The imbibed water of hydrogels provides a good medium for the transport of the water soluble species through the hydrogel, where the drug is incorporated by being either sequestered within the matrix or chemically bound to the polymer backbone[19].

Various biomedical benefits have been derived from transdermal drug delivery. These include: (i) The elimination of variables associated with oral administration such as pH, gastro-intestinal transit times, food presence and enzymes; (ii) improvement of systemic bioavailability resulting from bypassing hepatic first-pass metabolism; (iii) constant rate of delivery and (iv) easier application and removal of drug delivery device, eliminating the requirement of an injection.

The skin is a good candidate for drug delivery since it has the lowest enzymatic activity of all the delivery routes. However, the barrier properties of the skin limit permeation by passive diffusion to lipophilic drugs of small molecular size. The main obstacle to transdermal delivery of proteins or peptides is the impermeability of hydrophilic and ionic macromolecules across the skin by passive diffusion[23]. It may be necessary to alter the structure of the lipids in the skin in order to use a transdermal path for the delivery of large molecules[29].

Numerous skin permeation-enhancing techniques are available to improve skin permeation of drugs. For example, iontophoresis: increasing permeation of charged drugs into surface tissues by the application of an electric current for therapeutic purposes. This may increase the delivery of ionic, hydrophilic and high molecular weight drugs[30]. Additionally the use of ultrasound or benign penetration enhancers may improve skin permeability[28].

Controlled-release systems provide better regulated drug administration. Each drug has a therapeutic range above which it is toxic and below which it is ineffective. The aim of the controlled-release system is to ensure that the drug concentration remains in the therapeutic range for a prolonged time using a single-dosage form. However, this delivery suffers from the limitation that the release of the drug from the hydrogel follows first-order kinetics. The hydrogel exhibits a continuously diminishing rate of concentration with time. This is a consequence of increasing diffusional distance and decreasing area at the penetrating diffusion front.

A study of the release of Crystal Violet in phosphate buffer solution shows a faster drug uptake and release with semi IPNs compared to full IPNs. This is because additional cross-linking in the full IPN reduces the degree of molecular relaxation which in turn delays the permeation of the drug very extensively. This confirms that the synthesis of IPNs can change the drug-release timing and rate. The drug-release rate is enhanced with increased water content in the composition due to increased free volume of the hydrogel. Bromothymol Blue's release rate is more rapid in comparison to Crystal Violet's. This may be because of Bromothymol Blue's higher permeability due to its more hydrophilic nature or possibly Bromothymol Blue is more soluble than Crystal Violet in the phosphate buffer solution[1].

IPN structures that are sensitive to the external stimuli are of importance in applications of auto feedback delivery systems, e.g., thermosensitive hydrogels. The change in temperature induced by the presence of pathogens may be an important stimulus to the effective release of anti-hyperpyretic drugs for treatment of pyretic conditions. Delivery effectiveness is controlled mainly by the temperature sensitive swelling characteristics of the drug incorporating hydrogel e.g., poly (N-isopropylacrylamide). Hydrogels activated

by electric and magnetic fields, and pH have been widely studied and have shown good potential for future use as drug delivery devices[31,32].

1.13.2 Biosensors

The use of polymers as conductive materials was established by Mead and Fuoss in 1945, when they investigated the addition of electrolytes to plasticized PVC. By 1972 PVC-based ion-selective electrodes were being developed and in 1978, Hill *et al.* produced ion-selective electrodes using PVC membranes for *in vivo* studies of myocardial potassium ion concentrations. The highly plasticized PVC membranes acted as a liquid barrier and were important in the production of ion-selective electrodes because the PVC provided the structural framework of the network and the plasticizer facilitated the transport of ionophore and ion-ionophore complexes through the membrane[33].

Recently hydrogels have been used to provide an electrically conducting interface for biomedical sensors. The bioadhesive film can adhere to a biological substrate under adverse conditions such as high humidity or when the biological substrate is immersed in water or a biological fluid. The bioadhesive hydrogel forms a tack-free adhesive film eliminating the necessity for additional, surrounding, pressure-sensitive adhesives. Since the adhesive is moisture activated, it adheres to biological substrates under adverse conditions, for example, high humidity, where excessive perspiration can lead to the failure of conventional pressure-sensitive adhesive bonds.

The main advantages skin adhesive hydrogels have over conventional methods are the elimination of pathogens since all materials used are sterile and disposable. This removes the requirement of additional fluid to permit conduction as the gel contains all the necessary fluids within the matrix. Bioadhesives are also easier to apply and remove. These are the reasons why 90% of hospitals in the UK now use bioadhesive hydrogel biosensors.

Moisture-activated bioadhesive films derived from a copolymer of methyl vinyl ether and maleic acid are of particular interest as electrically conducting interfaces for biosensors. These films are applied in the dry state directly to the wet substrate and adhere

immediately on hydration. The interface of the bioadhesive films will gradually dissolve when in contact with water for prolonged periods. However, the interface can be made more durable by casting a thicker film from a higher viscosity blend formed by viscosity builders such as PVP. The addition of sodium chloride to render the cast films electrically conductive, had no significant effect on the adhesion of the resulting cast film interfaces. This is an essential property of the system, allowing secure attachment of the electrically conducting film interface to a wet substrate.

In agreement with the wet adhesion theory of Chen and Cyr, Woolfson showed there was an optimum film water content for maximum *in vitro* bioadhesion. This theory envisages bioadhesion as a dynamic process in which polymer chains are released from their restraints then interpenetrate with the substrate matrix. Maximum adhesive strength is attained when ideal matching occurs between the active adhesive sites on the polymeric chains and the substrate, increasing the magnitude of short-range dispersive forces. The entire process is hydration dependent.

Increased film storage temperatures at lower humidities were shown to decrease film bioadhesion significantly. Under these conditions, increased cross-linking of polymer chains are favoured. When subsequently hydrated, the polymer chains would no longer be free to uncurl and present their active bioadhesion sites[34].

The sensor-tissue interface has many stringent requirements which must be met. They include the absence of protein fouling, cellular and fibrous overgrowth, thrombus formation, inflammation and tissue necrosis. Glucose sensors must also be permeable to glucose.

Most biosensors are chosen for their electrical, mechanical or electrochemical properties. However, these materials may not elicit the desired biological response when implanted in the host. The materials coating the biosensor must adhere well to the outer material of the sensor, should allow the transport of the analyte and the products of its transformation and must elicit the desired biological response in the host. The protein adsorption and fibrous tissue encapsulation of Poly (ethylene glycol) has been investigated and indicates good biological performance in this polymer. Hence the

reason for its frequent use as a comonomer in hydrogel biosensors[35].

Investigations by Price and Hunter show promising results for the preparation of functionalised membranes for chemical sensors. Their work has shown that polymerisation of micro-emulsions containing functionalised monomers can yield micro porous membranes with high surface areas, enabling them to act as absorbents for example for metal ions from aqueous solution[36].

Donat *et al,* produced results confirming conduction occurs via inter-cluster hopping. The nature of the hopping condition depends on the material. Conductivity is enhanced by three-dimensional ordering due to a large delocalisation length along the main chain. This three-dimensional ordering results from local ordering between the lateral alkyl groups. Conduction is also temperature dependent[37].

There are many biomedical applications of hydrogel sensors. Examples include electrodes for the monitoring of foetal heart rate and other physiological and analytical sensors such as electrocardio-gram ECG, electroencephalogram EEG, electro-myogram EMG used to stimulate a subject for transcutaneceous electrical nerve stimulation, wound healing, muscle stimulation, external pacing, defibrillation or even for iontophoresis of drugs into a patient [38].

1.13.3 Wound Dressings

Skin adhesive hydrogels can be used as wound dressings for the treatment of burns, dermatitis, ulcerations, blisters, herpes and other skin conditions. Wound dressings should be flexible, strong and non-antigenic. Additionally the wound dressing must be permeable enough to allow the movement of water vapour and metabolites yet should cover the wound sufficiently to prevent bacterial infection[19].

1.13.3.1 Natural Hydrogel Wound Dressings

Natural hydrogel polymers have been investigated for use as wound dressings, but their poor mechanical strength usually requires them to be used in conjunction with a fibre or

polymer matrix for support. Some examples of natural hydrogel dressings used with a support matrix includes dextran-based hydrogels reinforced with fine cotton gauze, sugar and protein derivatives radiation cross-linked with acrylic acid and bonded to supporting film and copolymers of water soluble, linear anionic and cationic polyelectrolytes such as ammonium keratinate and chitosin or collagen. When the materials are hydrated, they become more malleable and can be shaped to the contours of the wound[19].

1.13.3.2 Synthetic Hydrogel Wound Dressings

Several synthetic hydrogels exist such as the pluronic based systems, the latter consists of a block copolymer of polyoxypropylene glycol, and ethylene oxide, with water soluble oxyethylene chains (70%) at the ends and insoluble oxypropylene chains in the centre (30%). At low temperature, this solution is a liquid that can be poured onto the wound site. At body temperature, the solution forms a clear gel which fills the wound crevice and prevents bacterial infection. Examples of wound dressings include a US patents 5,674,523 and 5,762,620 by Carmell. The wound dressing contains a partially dehydrated hydrogel in the form of a gauze, with no backing or adhesive layer. The partially hydrated hydrogel absorbs wound exudate without inhibiting the healing process[19].

1.14. Introduction to Skin

The composition of skin, the principal lipids within the skin layers, and the problems of individual variation of skin lipids are described in depth. This enables the difficulties of producing an adhesive hydrogel which can be used on a diverse range of individuals to be addressed and the information may assist in making a skin model.

1.14.1. The Composition of Skin

The skin is the largest organ in the body, comprising 10% of the body weight. In addition, this organ contains a circulatory and evaporation system, serves as a barrier to pathogens and helps regulate the temperature of the body. The skin has an elaborate, orderly construction composed of three layers, the stratum corneum, the granular cells

and the basal cells which form the outer, middle and innermost layers respectively. The stratum corneum (the external layer) is a nonviable layer[38]. The layers are primarily composed of protein, lipids and carbohydrates. A diagrammatic representation of the stratum corneum (10μm), the viable epidermis (75-150μm), dermis (3-5mm) and subcutaneous fat is illustrated in figure 1.7[16].

The main protein in skin is collagen (type I, III and V), a family of proteins which form insoluble fibres that have a high tensile strength. Collagen contains a distinctive amino acid sequence in which nearly every third residue is glycine, likewise, a high proportion of proline is also incorporated[29]. Glycosaminoglycans, the polysaccharide chains in proteoglycans, include chondrion-6-sulphate, dermatan sulphate and hyaluronic acid, each possess at least one sugar with a negatively charged carboxylate or sulphate group. Condrion-6-sulphate and dermatan sulphate contribute to reinforce the mechanical strength of collagen and decrease cell proliferation. Condrion-6-sulphate also increases collagen's resistance to collagenase[39]. The carbohydrates exist in many forms either attached to the proteins to produce glycoproteins or to the lipids to make glycolipids[29]. The lipids are very important and vary greatly between layers. It is the lipids which play a major role in adhesion by causing the skin to be either sticky or non-sticky.

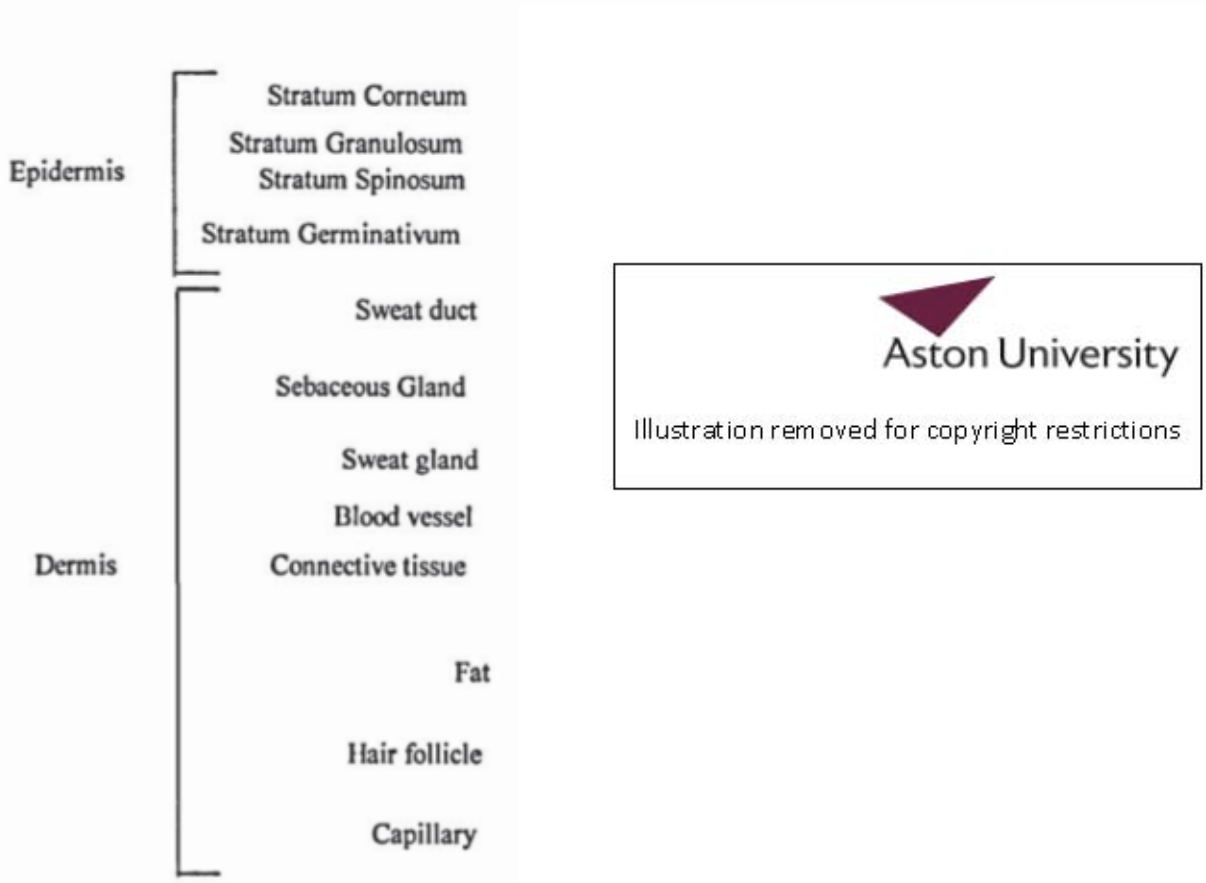


Figure 1.8 Schematic cross-section of the uppermost layers of human skin, showing the stratum corneum, the epiderims and the dermis, including the sweat glands and hair follicles[16].

1.14.2. The Lipid Composition of the Skin Layers

In 1932, Kooymann demonstrated that epidermal lipid composition alters as a function of differentiation. This was revealed by the striking difference in the phospholipid content of stratum corneum compared to viable epidermis[40]. It was Long who observed a gradual increase in cholesterol and free fatty acids in going from the basal layer to the stratum corneum, unlike the phospholipids which accumulate in the basal layer and granular cells but are degraded in the stratum corneum[41]. Nicolaides[42] identified ceramides as the major polar lipid component of the stratum corneum, however, this fact was ignored prior to the studies of Gray *et al.* in 1970[43-45].

Gray and his co-workers isolated cell fractions enriched in basal cells, granular cells and stratum corneum by tryptinisation and performed a detailed lipid analysis. Their findings revealed that basal cells contained a small amount of cholesterol and a large amount of phospholipids, in particular phosphotidylethanolamine, phosphatidylcholine and sphingomyelin. The mature granular cells contained additional cholesterol and phospholipids, as well as ceramides, glucoceramides and free fatty acids. In progression from the granular cells to the stratum corneum, the phospholipids were completely degraded and the glucoceramides were deglycosylated leaving ceramides, cholesterol and free fatty acids as the major lipids. Additionally, small amounts of triglycerides and cholesterol esters were found.

Layer	Composition
Stratum Corneum	Ceramides, cholesterol and fatty acids, with a small proportion of cholesterol esters and triglycerides
Granular cells	Phospholipids, cholesterol, glucosylceramides ceramides, and free fatty acids
Basal cells	Phospholipids, especially sphingomyelin, phosphotidylcholine and phosphotidylethanolamine and a small proportion of cholesterol

Table 1.3 A summary of the lipid composition of the three individual skin layers.

The skin layers show a gradual modulation of lipid composition and not abrupt changes. Gray and Yardley confirmed this with subsequent studies in which lipid analysis was performed on 10μm thick slices cut parallel to the plane of the epidermis from frozen skin[46,47].

1.14.3 The Stratum Corneum

The stratum corneum is of particular interest as it is the surface which will be presented to the adhesive material. Therefore, its composition has been examined in more detail. The stratum corneum consists of:

- 10-15% free fatty acids. The free fatty acids are mainly straight chain and saturated. They are of 14-28 carbons in length with 22 and 24 carbons being the most abundant. The free fatty acids and cholesterol sulphate are the only ionisable lipids in the stratum corneum and may be required for bilayer formation.

- 25% cholesterol and 5% cholesterol sulphate. Small amounts of cholesterol ester, cholesterol oleate and ester linked α hydroxy acids are present. They are non-bilayer forming.

- 50% ceramides. There are 6 different types of ceramides, all structurally heterogeneous, which account for half of the total lipids in the stratum corneum.

All the aliphatic chains in the ceramides and fatty acids are straight and all of the polar heads are minimal in size.

1.14.4 Skin Contaminants

There are two major skin contaminants these are alkanes and sebum.

1.14.4.1 Alkanes

Further components exist in the skin layer in addition to the usual lipids, proteins and carbohydrates. They are considered to be contaminants. Gray and Yardley[44] discovered alkanes among the epidermis, however, they suspected the alkanes were environmental contaminants rather than epidermal lipids. Evidence to confirm their suspicions came when the metabolism of radio-labelled acetate was injected into porcine epidermis. The acetate was incorporated into the lipids but not into the alkanes[48]. This evidence was supported by the fact that the occurrence of alkanes in porcine stratum corneum was highly variable from one specimen to another[49]. Studies on human stratum corneum revealed the alkane content of lipids collected from the leg of 15 subjects contained 0.5-1.7%, but in 5 out of 6 of the same individuals there were no alkanes in the ear wax, suggesting that the alkanes were derived from surface contaminants. Additionally, the

chain length distribution differed dramatically from one subject to another and they all resembled petroleum fractions. Finally the alkanes were proved not to be of recent biogenic origin by carbon dating[50].

1.14.4.2 Sebum

The second source of contamination, sebum, particularly affects the stratum corneum. In humans, the sebaceous glands produce a liquid phase lipid mixture consisting mainly of squaline, wax esters and triglycerides[51]. Small amounts of cholesterol and cholesterol esters are also present. This mixture flows through the follicles and over the skin surface where the triglycerides are acted upon by microbial and epidermal lipases to liberate free fatty acids. These fatty acids range from 10-18 carbons in length and generally C16:0, C16: 1 Δ 6 and C18: 1 Δ 18 are the most abundant species, methyl branched fatty acids are also present. The extent of triglyceride hydrolysis is highly variable from one specimen to another[52].

1.14.5 Surface Skin Lipids

The sebum composition differs depending on the location of the body, predominantly due to the sebaceous gland density and hormonal sensitivity in that region. Monti *et al.* analysed the surface skin lipids of the forearm and the forehead of ten volunteers by separated thin layer chromatography and by quantified computerised scanning densitometry. The two regions present both the sebaceous and keratinocyte derived lipid component. The results showed that the overall skin surface lipid on the forehead is fivefold higher than on the forearm and the sebaceous content was two fold higher on the forehead. This study demonstrates that the ratio between sebaceous lipids and keratinocyte lipids of the skin surface lipids is fixed for the different skin areas and contributes to skin homeostasis[53].

S. Motta *et al.* studied the sebaceous lipids by two different extraction methods. The sebaceous glands that had been extracted from the abdominal skin, were subjected to overnight extraction with Blight-Dryer solvent and subsequently the supernatant was

processed for lipid extraction. Subsequently, the same gland pellet was re-suspended in new Blight-Dryer solvent and sonicated. The filtered solution was then processed for lipid extraction. Lipids obtained by the two different extraction techniques were separated by thin layer chromatography and quantified by computerised scanning densiometery. Wax esters and squalene were found to account for 30% of the total lipid ceramides, while free fatty acids account for 50%. This study demonstrates that *in vivo* pure sebaceous lipids, without keratinocyte lipids, cannot be obtained even from isolated sebaceous glands. When collecting skin surface lipids a mixture of sebaceous and keratinocyte lipids is obtained[54].

Quantification of skin surface lipids by enzymatic assay has revealed large variations in surface skin lipids between women with acne, different age or stages in their menstrual cycle. Glycerol esters and free fatty acids increased with age until women reached their thirties, decreasing thereafter. Cholesterol however, did not change in quantity until they reached fifty, there after it declined. Cholesterol and its esters are derived from the epidermal cells and do not appear to be as strongly influenced by hormones which effect the other lipids derived from the sebaceous glands.

Women with acne have a notable increase in skin surface lipids compared to women without acne. The glycerol esters in the skin are comprised of triglycerides, diglycerides, monoglycerides and glycerols. Free fatty acids are released during the degeneration of triglycerides into diglycerides, monoglycerides and glycerol due to the action of lipases as mentioned previously. The increased amount of glycerol esters and free fatty acids indicates an increase in triglycerides production in the sebaceous glands, with an increased breakdown into free fatty acids.

In the women with acne, significantly greater amounts of cholesterol, glycerol esters and free fatty acids were observed in the pre-menstrual group of women, opposed to those who were menstruating. No significant change was observed in those women without acne[55]. Serum testosterone, dihydroepiandrosterone are and dihydrosterone are higher in female acne patients than healthy controls, especially in the luteal phase of the menstrual cycle which act to elevate sebum production.[56]

The skin surface presented to the bioadhesive will vary depending on the position placed on the body, the individual's skin condition (pH, moisture content, acne, etc.) age, hormone levels, exposure to skin contaminants and possibly menstrual cycle. Therefore, all these variations must be considered when designing a bioadhesive to suit the majority of skin types.

1.15.Bioadhesive Hydrogels

Bioadhesive hydrogels are hydrogels possessing adhesive properties to biological surfaces. Adhesion is defined as the state in which two bodies, in the form of condensed phases, are held together for an extended period of time by interfacial forces. These forces may range from valence forces to mechanical interactions, or some combination of chemical and physical interactions. Adhesion is referred to as bioadhesion, if one or both of the adherends are of biological nature. A bioadhesive can therefore be defined as a substance which has the ability to interact with biological material and is capable of being retained on the biological substrate for a period of time. One distinctive feature of bioadhesion is that adhesion almost always occurs in the presence of water[57].

1.16 Conventional Biosensors

The first signal collection systems as described in U.S. patent 4,016,869,[58] involved an electrode being pasted onto the body by means of a crossed-over adhesive foil. Preceding the application of an electrode, an adapted contact gelatin (gel) is added to improve the conduction between the electrode and the skin. This system is cumbersome and pain can be experienced when tearing off or repositioning the adhesive foil.

Other earlier systems for collecting the body's electrical signals consisted of at least one electrode adhered to the body by a conducting paste. The homogeneous contact paste and adhesive has a syrup like consistency and were applied directly to the body, with the electrode placed on top. The conducting paste is of particular interest as it resembles the hydrogels which are currently used for skin adhesive purposes, as in U.S. Patent No. 4,593,053 by Jevne *et al.* [59].

The paste uses polyethylene glycol as its principal material to provide a viscosity low enough for easy application to the skin and yet sufficiently high to achieve a good adherence with the electrode. Furthermore the polyethylene glycol paste is non toxic and can accommodate temperature fluctuations between 20 and 45 degrees Celsius without altering its function, in addition to being storable for lengthy periods without variations in consistency due to drying out, separation or spoilage, for example, due to the presence of micro organisms.

The conducting paste consists of 50% PEG 200 and 35% PEG 6000 with a 10% conducting solution of NaCl, containing 0.1M NaK/tartrate as a depolariser, and 5% cetylalcohol as an emulsifier. Alternative combinations of PEG can be used to create a conducting paste of similar properties. Using conducting paste to adhere the electrode to the body was an improvement on earlier systems, however, this system has many drawbacks.

The conductive creams, pastes or gels are unpleasant to use as they can be sloppy and cause irritation to the skin because of their ionic nature, particularly when the skin is cleaned and abraded prior to application of the electrode. These electrodes all contain water as the major ingredient to solvate the ions present and function as a medium through which the solvated ions migrate, they therefore require elaborate packaging to prevent loss of water prior to use. Furthermore these electrodes leave a residue on the skin which requires removal and if expensive silver/silver chloride is not employed on the surface of the plate, an over potential occurs during defibrillation procedures.

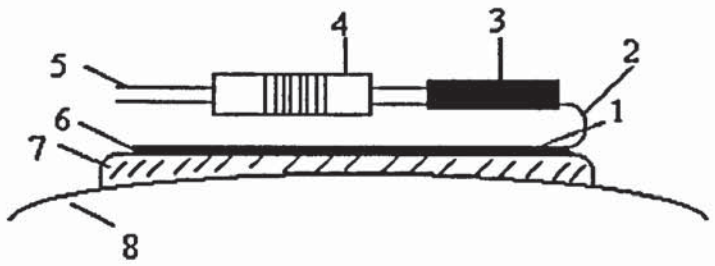


Figure 1.9 Illustrates the side view of a signal collector system invented by Reichenberg.

1 - A thin stainless steel electrode e.g. NiMo-steel.

2 - A socket connector

3 - The plug connector

4 - The banana plug of a signal cable

5 - A socket connector

6 - The cable end point

7 - The contact paste

8 - The skin

The "wet" electrodes have been superseded by "dry" electrodes, electrodes which utilise dry conductive material. The dry electrodes offer several advantages over conventional prior art electrodes. For example, as major amounts of water are not required expensive packaging can be eliminated and only a covering to protect the adhesive surface is required. Application of the electrode to the body is not messy and no residue remains on the skin. The skin does not need to be primed with alcohol prior to electrode application preventing possible skin irritation. Neither does the skin need to dry completely before applying the electrode because the adhesion of the electrode to the skin is enhanced by moistened the skin. Furthermore, no costly surface treatment of the electrode plate is required in order to render it suitable for use in connection with defibrillation procedures.

For the dry electrodes to be comfortable they must be sufficiently compliant to conform to the surface of the skin beneath the plate in order to provide a high surface area of contact between the skin and the electrode. The film-forming material must also be more cohesive than adhesive so that on removal of the electrode from the skin, the conductive layer remains intact and does not remain on the skin.

Numerous dry electrodes exist. U.S. Patent by Larimore *et al* [60] No. 4,273,135 references U.S. Patent No 3,993,049 which discloses a biomedical electrode having a salt dispersed adhesive layer which secures the electrode to the skin, enabling the salt to serve as a current carrier. Preferably, the salt used contains a cation of the metal that forms the surface of the electrode plate, for example, sliver halide with a silver electrode plate. Additionally, it is preferred that the adhesive includes metal powders or is adhered

to a metal plate. The adhesive layer requires a salt solution and metal powders to obtain an acceptable electrical conductivity. However, this may increase the possibility of skin irritation.

Other electrodes exist which employ natural polymers such as gum karaya, for securing the electrode to the skin. Gum karaya is a complex polysaccharide combined with certain metallic cations such as sodium, potassium, calcium or magnesium. The gum does not dissolve but swells in water to a paste-like gel. It must be noted that due to their natural origins, such polymers are variable in nature as a result of soil and climatic conditions under which they are collected and processed. This leads to inconsistency in the physical and chemical properties of the natural polymers and the amount of impurities present, resulting in variations in the electrical performance of biomedical electrodes fabricated from such polymers.

Despite the obstacles involved when working with gum karaya, successful patents do exist such as U. S. Patent No. 4,391,278[61]. These patents claim conduction to be acceptable and is enhanced as the electrode ages whilst in contact with the skin. Such patents also give examples of other materials added to karaya to enhance the properties of the electrode. For example the mechanical properties can be enhanced by the addition of protein, starch, cellulose, Poly (vinyl chloride), urathane, epoxy resins, certain polyesters and calcium salts.

Although many diverse patents claim to satisfy the criteria required for a dry skin adhesive electrode, the process by which the solvent free synthetic adhesive electrodes are created usually involves analogous steps, as described in U.S. Patent No. 4,554,924[62]. These steps involve (1) forming an adhesive precursor comprising (a) a water soluble polyhydric alcohol which is a liquid at room temperature (e.g. glycerol), (b) an ionic unsaturated free radical polymerisable material which is soluble in the polyhydric alcohol, (c) a free radical initiator which is soluble in the polyhydric alcohol, and (d) a multifunctional unsaturated free radically polymerisable cross-liking agent; (2) coating the adhesive precursor on one side of an electrode plate (conductive sensing element); and (3) polymerising the coated precursor *in situ*.

Three different dry electrodes all produced in the 1980s were selected to show the diversity between electrode shapes, attachment points and conductive material. In 1981, Hymes[63] produced a monitoring and stimulation rectangular electrode U.S. Patent. No. 4274420 which used aluminium foil as the main conductive material with a snap fastener as an attachment point. In 1985, U.S. Patent. No. 4554924 by Engel established a circular electrode utilising silver as its main conducting material and a snap connection point. The late eighties, a square electrode employing tin as its main conductive material and a U shaped tab as a connection point was revealed in U.S. Patent. No. 4674512[26] These electrodes are all shown below in respective order.

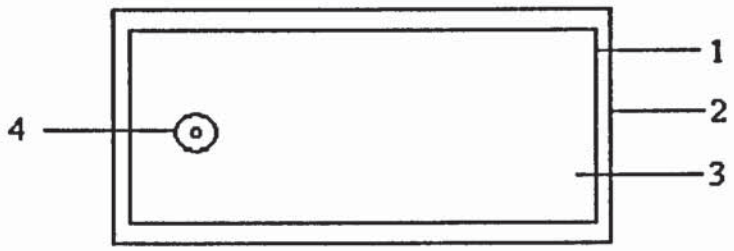


Figure 1.10 An elevation view of a stimulation electrode, U.S. Pat. No. 4,274,420.

1 - A conductive support and electrical current distribution member

2 - An electrically conductive and adhesive material

3 - A conductive support member made of aluminium foil

4 - An electrically conductive swaged snap fastener

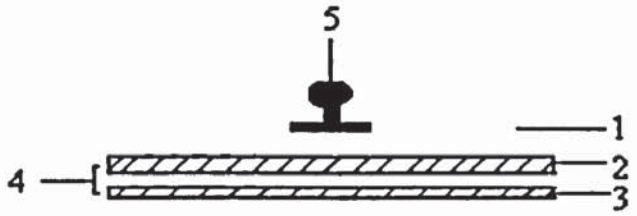


Figure 1.11 An exploded sectional view of a disposable ECG electrode containing a conductive adhesive, U.S. Pat No. 4,554,924.

1 - A disposable ECG electrode

2 - A non-woven web

3 - A silver vapour coat on the under side of 2

4 - The electrode plate consisting of 2 and 3

5 - Stainless steel stud

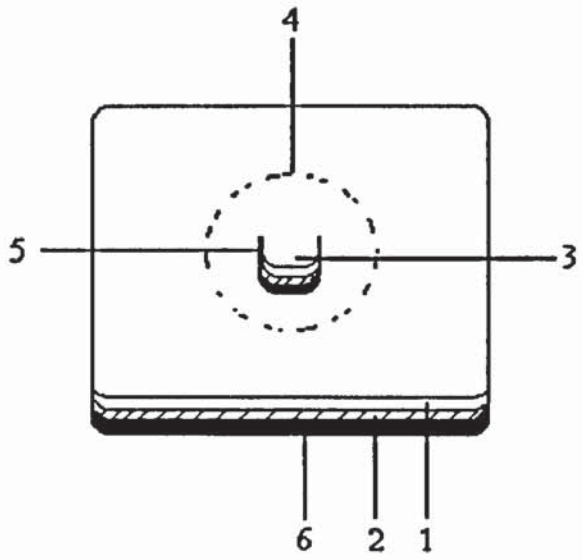


Figure 1.12 A perspective view of a medical electrode, U.S. Pat. No 4,674,512.

1 - Pressure sensitive tape

2 - Pressure sensitive surface to adhere to the skin

3 - U shaped tab

4 - Conductive layer/flexible tin layer

5 - Flexible substrate matrix

6 - Removable protective layer

An ideal electrode or sensor should contain the minimum number of layers possible. Many layers are undesirable because they bring about numerous problems, for example: several layers of material increases production cost, the soluble substances can diffuse from one layer to another enabling chemical changes to occur during shipment or storage, the layers add bulk and may not contribute to carrying current and de-lamination

is possible. To reduce costs electrodes should be produced from conductive tinfoil instead of silver/silver chloride but not at the expense of stability or heterogeneity. Two effects should be exhibited by the electrode, the first being rapid depolarisation of charged internal layers caused by defibrillation pulses and the second being a relatively low and constant DC offset and a constant impedance with the fluctuating voltage applied at various frequencies. Low impedance is important because it will provide a higher signal to noise ratio. The matrix which is coated on the lower surface of the electrode should be homogeneous and hydrophilic to enable uniform electrical conduction, self supporting so it retains its shape without assistance and sufficiently pliant to conform to the shape of the body contours and establish good electrical contact.

The most recent patents from Anderson *et al.*, Tang *et al.* and Perrault, US Pat. Nos. 5,645,052, 5,674,275 and 5,800,685 respectively, have produced improved quality skin adhesive electrodes of improved quality. These patents claim their adhesive hydrogels described can be used alone, without a conventional pressure-sensitive adhesive to secure the electrode to the skin. This is a result of the hydrogel's own specific adhesive properties and in particular high peel strength, since, low peel strength provides less secure attachment of devices to the patient allowing easier removal of the hydrogel adhesive. Depending on the particular function, varying hydrogel adhesive peel strengths are required.

These hydrogels possess repositionability, i.e. the ability of the adhesive hydrogel to be removed from one area of the skin and attached to another area without loss of peel adhesion properties. Other properties of the adhesive used include tack adhesion and creep compliance.

The patents also recognise that the nature of the cross-linked water soluble polymer used in the hydrogel adhesive can determine the properties of that adhesive. In order to vary the peel strength or repositionability of the adhesive, different water soluble polymers may be used. Development of the hydrogel properties is an empirical process at present. A water soluble polymer system that allows a broad range hydrogel adhesive properties without changing the type of polymer used is most desirable.

Permeability is also noted as being important, and it refers to the ability of the adhesive, in conjunction with the substrate, to pass moisture absorbed from a patient's skin through the adhesive and the substrate and out of the system to the surrounding atmosphere. This prevents weakening of the bond strength of the adhesive and injury to the skin.

An adhesive material when in contact with the body typically absorbs moisture from skin. This absorbed moisture generally weakens the bond strength of the adhesive to the skin especially if the adhesive is occlusive. If a gas permeable substrate is used behind the hydrogel adhesive, moisture adsorbed from the skin surface can pass from the hydrogel adhesive to the gas permeable substrate. Moisture may also evaporate from the sides of the gas permeable substrate and the hydrogel. Evaporation of moisture maintains a balanced moisture level at the adhesive-skin interface, which is essential for long term adhesion of a device to the skin.

Another advantage of using hydrogels on gas permeable substrates is that moisture does not accumulate at the adhesive-skin interface which may cause skin maceration, irritation, discomfort and bacterial proliferation. The hydrophilic nature of these hydrogels and the use of water as a solvent means that water transmission inside the hydrogel adhesive is virtually unrestricted. The water movement within the gel depends on the type of skin, the environment e.g. temperature and humidity, the hydrophilicity of the hydrogel and the water vapour transmission rate of the substrate.

Tang *et al.* use ionic monomers identical and similar to the ionic monomers investigated in this thesis for example SPA, they also use the photoinitiator Darocure 1173 as does Perrault who also uses Irgacure 184, a photoinitiator used throughout this thesis. The more recent patents use similar ionic monomers and photoinitiators investigated later in this thesis[64-66]. This suggests that a limited number of ionic monomers can be incorporated to produce hydrogels with optimal adhesive properties.

1.19 Aims and Objectives

The overall aim of this study is to determine what properties a gel must possess to be a good skin adhesive material and to establish how these properties are measured. These gels can subsequently be tailored for use in many applications, such as biosensors and drug delivery devices. Currently there is limited literature on skin adhesives, although this is a rapidly developing area. Therefore it is essential to make and study basic non adhesive hydrogels to learn the fundamental factors governing hydrogel hydrophilicity before investigating the additional properties which may influence hydrogel adhesion to skin.

The first steps involve analysing the properties of ionic monomers to decide which monomers are best used as skin adhesives. The main ionic monomers investigated were; the potassium salt of (3-sulphopropyl)-ester of acrylic acid (SPA), the potassium salt of N,N-Dimethyl-N-methacryl-oxyethyl-N-(3-sulphopropyl)-ammonium-betaine (SPE), the potassium salt of (3-sulphopropyl) ester of itaconic acid (SPI); N,N-Dimethyl-N-methacryl-amidopropyl-N(3-sulphopropyl)-ammonium-betaine(SPP),1-(3-Sulphopropyl) 2-vinyl pyridinium-betaine (SPV) and the sodium salt of acrylamido methylpropane sulphonate (NaAMPS) in the form of copolymers with water soluble interpenetrant polymers, hydroxy propyl methyl cellulose, and low molecular weight polyethylene glycol methacrylates. Combination of ionic monomers were studied to deduce the effect on hydrophilicity of the resultant gel. It was thought that combining hydrophilic monomers may give free chains to enable hydrophobic interactions to occur on the surface of the hydrogel and hence increase skin adhesion.

The relative hydrophilic potential of the resultant gels are determined by fully hydrating them even though they are only likely to be partially hydrated in their skin adhesive applications. The gels are subsequently examined by differential scanning calorimetery to determine the percentage and states of water in the sample and furthermore mechanically tested to measure gel strength.

The monomers showing the greatest hydrophilic potential, shown by their EWC, were then examined for use as skin adhesives. This entails adding the selected monomers to a selected formulation high in glycerol and of moderate water level.

For a hydrogel to be suitable for use as a skin adhesive, the gel must have a good appetite for water to prevent the water from accumulating between the skin and the hydrogel and lubricating the interface, should have the appropriate mechanical properties so as to be sufficiently strong and comply with the skin, yet not be too rigid and residue should not leak from the polymer. When gels showing good potential as a bioadhesive were produced, their adhesiveness was tested initially by touch and then by peel testing.

A series of skin models were prepared to attempt to produce a realistic substrate on which to test the peel strength of the bioadhesives synthesised. An adapted peel test was developed to enable comparative results of the peel strength of the bioadhesives to be determined.

The most cohesive and adhesive hydrogels were subsequently characterised to determine what comprises a good skin adhesive. This was accomplished by determining properties such as the surface energy of the hydrogels by contact angle measurement using a goniometer, dynamic mechanical properties by use of a rheometer, and adhesive properties by means of the 90 degree peel test.

Having defined parameters which determine the skin adhesive efficacy of a hydrogel is a good skin adhesive, the effect of adding other monomers such as acrylic acid and a polymer emulsion for instance poly (ethylene-co-vinyl acetate), was investigated.

Skin damage caused by peeling was investigated by scanning electron microscopy of pressure sensitive adhesives that had been removed from the body and skin adhesive hydrogels which had been peeled from the body and critical point dried. This was performed to observe the effect of gels being used repeatedly on the skin.

Chapter 2

Materials and Methods

2.1 Reagents

The reagents used in this study are shown in the following table 2.1 (as listed at the foot of page 73). Their structures are shown in figure 2.2.

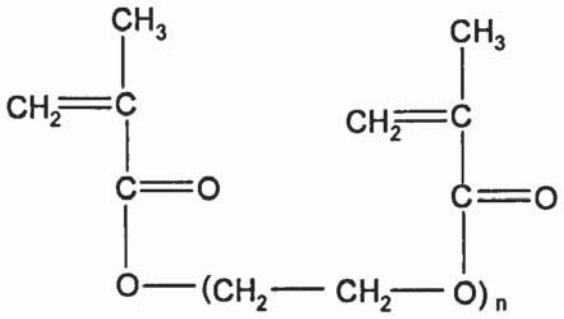
Reagent	Molecular weight	Abbreviation	Supplier
Acrylamide	71	None	B.D.H.
Acrylic Acid	72	None	Aldrich
Ebacryl II	Confidential	None	U.C.B.
Formaldehyde	30	None	Fisher Science
Gelatine	Not stated	None	Hopkin & Williams
Glycerol	92.1	None	Fisons
Gum Karaya	9,500,000	None	Sigma
Gum Locus Bean	310,000	None	Sigma
Gum Xanthan	Not stated	None	Sigma
1-Hydroxycyclohexyl phenyl ketone	204.3	Irgacure 184	Ciba
Hydroxypropyl methyl cellulose	12,000	HPMC	Aldrich
IRR-210	Confidential	None	U.C.B
N,N'-Methylene-bis acrylamide	154	M bis A	Sigma
N-iso-propyl acrylamide	113	NPA	Polysciences Ltd.
Sodium 2-acrylamido 2-2 methylpropane sulfonic acid	229	NaAMPS	Lubrisol
Poly (ethylene-co-vinyl-acetate)	98	DM 137	
Poly(ethyleneglycol) 200 dimethacrylate	354	PEG 200DM	Polysciences Ltd.
Poly(ethyleneglycol) 400 dimethacrylate	554	PEG 400DM	Polysciences Ltd.
Poly(ethyleneglycol) 600 dimethacrylate	754	PEG 600DM	Polysciences Ltd.
Poly(ethyleneglycol) 1000 dimethacrylate	1154	PEG 1000DM	Polysciences Ltd.

Reagent	Molecular weight	Abbreviation	Supplier
Poly(ethyleneglycol) 200 monomethacrylate	285	PEG 200MMA	Polysciences Ltd.
Poly(ethyleneglycol) 400 monomethacrylate	485	PEG 400MMA	Polysciences Ltd.
Propyl 4-hydroxybenzoate	180.2	PHB	Aldrich
Silastic 3481 base	Confidential	None	Dow Corning
Silastic 81-VF curing agent	Confidential	None	Dow Corning
Sodium hydroxide	40	NaOH	Aldrich
Acrylic acid-bis-(3-sulfopropyl)-ester, potassium salt	232.2	SPA	Rashig
N,N-dimethyl-N-methacryloyloxy-ethyl-N-(3-sulphopropyl)ammonium betaine	279.1	SPE	Rashig
Itaconic acid-bis-(3-sulfopropyl)-ester, di-potassium salt	450.6	SPI	Rashig
N,N-Dimethyl-N-methacrylamido-propyl-N-(3-sulfopropyl)-ammonium-betain	292.1	SPP	Rashig
1-(3-Sulfopropyl)-2-vinyl-pyridinium-betain	227.1	SPV	Rashig
Thixo additive	Confidential	None	Rep. Tech. Ltd.
Trimyristin	723.2	None	Sigma
Uranyl nitrate	394	None	Fisons

Table 2.1 The abbreviations and suppliers of the reagents used.

2.2 Monomer Structures

2.2.1 Poly(ethylene glycol)

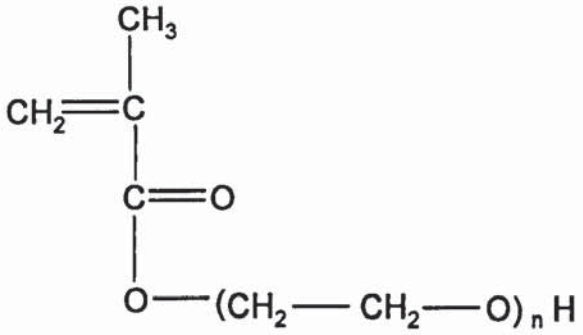


n = 4 to 5 Poly(ethylene glycol) 200 dimethacrylate

n = 9 to 10 Poly(ethylene glycol) 400 dimethacrylate

n = 13 to 14 Poly(ethylene glycol) 600 dimethacrylate

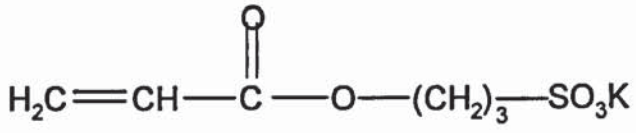
n = 22 to 23 Poly(ethylene glycol) 1000 dimethacrylate



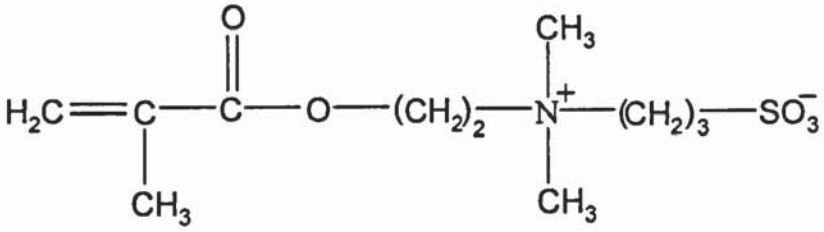
n = 4 to 5 Poly(ethylene glycol) 200 monomethacrylate

n = 9 to 10 Poly(ethylene glycol) 400 monomethacrylate

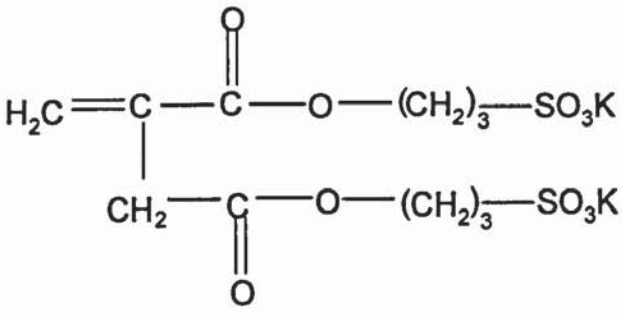
2.2.2 Ionic Monomers



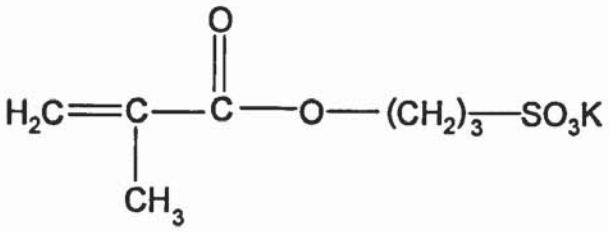
Potassium salt of 3-sulfopropylester acrylate (SPA)



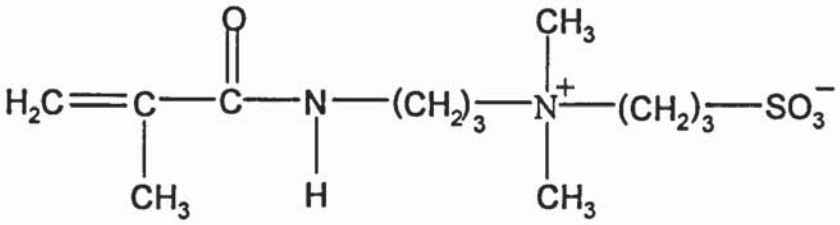
N,N-Dimethyl-N-methacrylate-oxyethyl-N-(3 sulphopropyl) ammonium betaine (SPE)



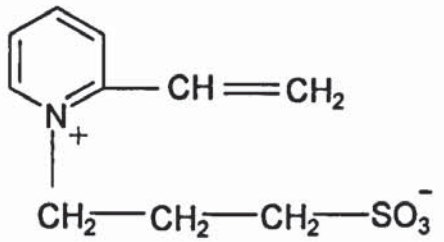
Di-potassium salt of bis-3-sulfopropylester acrylate (SPI)



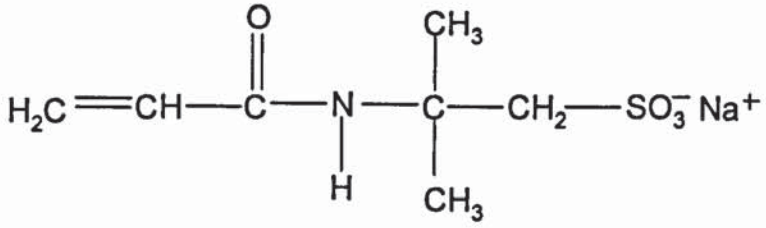
Potassium salt of 3-sulphopropylester methacrylate (SPM)



N,N-Dimethyl-N-methacrylamido-propyl-N-(3 sulphopropyl) ammonium betaine (SPP)

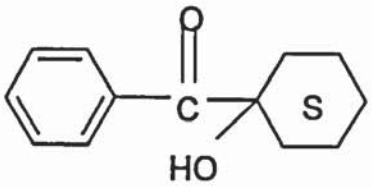


1-(3-Sulfopropyl)-2-vinylpyridinium-betaine (SPV)

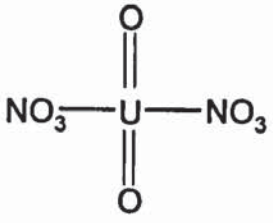


Sodium 2-acrylamido 2-2 methylpropane sulfonic acid (NaAMPS)

2.2.3 Photoinitiators

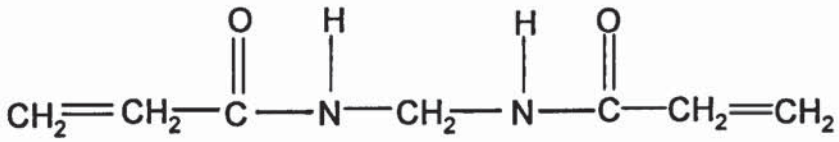


1-Hydroxycyclohexyl phenyl ketone (Irgacure 184)



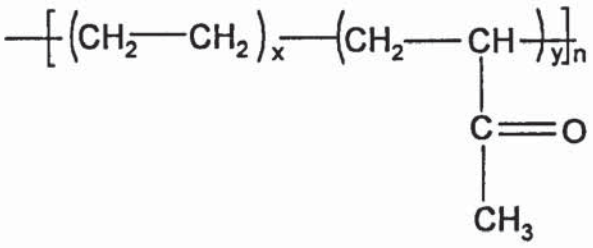
Uranyl nitrate

2.2.4 Cross-linker



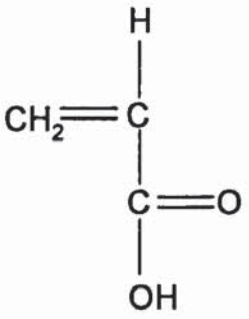
N, N-Methylene-bis acrylamide

2.2.5 Polymer Emulsion

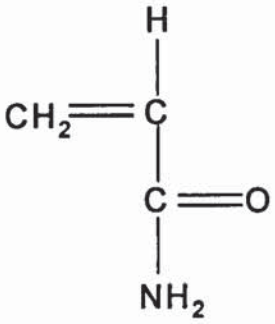


Poly (ethylene-co-vinyl-acetate) (DM 137)

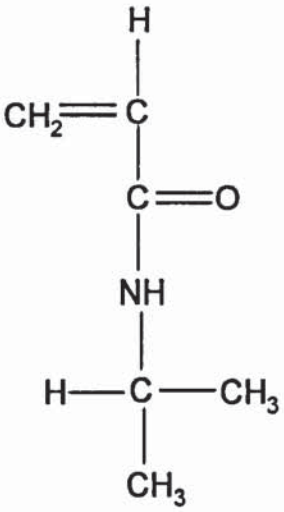
2.2.6 Acid and Acrylamides



Acrylic Acid

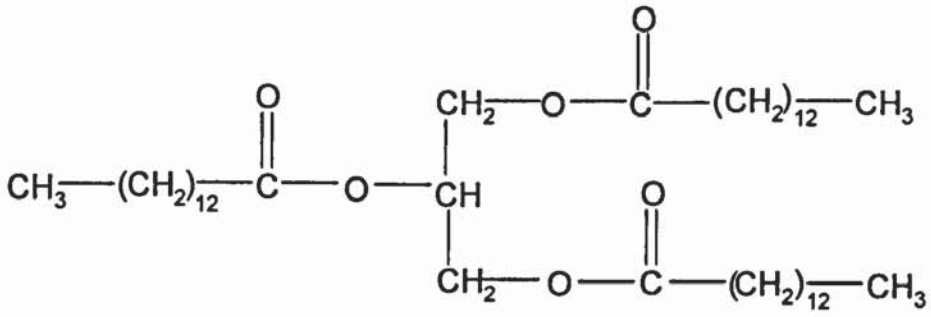


Acrylamide

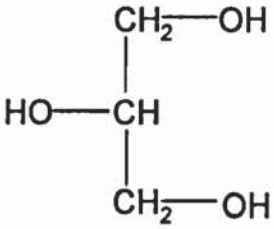


N-iso-propyl acrylamide

2.2.6.Lipid and Diluent

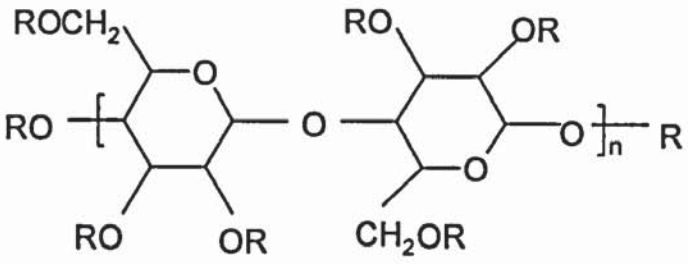


Trimyristin



Glycerol

2.2.7 Interpenetrant



R =.$CH_2CH(OH)CHCH_3$, CH_3 or H

Hydroxypropyl methyl cellulose (HPMC)

2.3 Preparation Of Membranes

2.3.1 Fully Hydrated (Non Adhesive) Membranes

Non adhesive membranes are produced by UV polymerisation of the monomer mixture between a glass mould as shown in figure 2.1. Two glass plates (15cm x 10cm) were each covered with a "Melinex", [(polyethylene terephthalate)] sheet to permit easy separation of the polymer membrane from the plates. Two polyethylene gaskets (each 0.2 mm thick) were placed upon one of the melinex sheets. The polymer solution was poured onto the melinex sheet between the space provided by the two gaskets. The other glass plate was placed on top with the melinex side down and spring clips were used to hold the mould together. Usually membrane preparation requires the insertion of a G22 syringe needle for the injection of the monomer mixture into the mould cavity. However, due to the viscosity of the polymer mixtures used, this was not possible.

To prepare a typical non adhesive membrane, 5g of monomer mixture were mixed together in an IKA VIBREX VXR shaker to obtain a homogeneous solution to which 1.0% (w/w) methylene bis acrylamide, a cross-linker, and 1.0% (w/w) Irgacure 184, a photoinitiator was added. The mixture was sonicated to remove any air bubbles, poured into the mould and subsequently placed under a medium intensity mercury lamp at 175 Watts for approximately 20 minutes. On completion of polymerisation, the spring clips were removed and, after opening the mould, the membrane was separated from the Melinex sheets. The membrane was then placed in distilled water to hydrate for at least five days. Previous studies with a variety of monomer combinations have shown that, provided the hydration medium was changed daily, constant values of equilibrium water content were reached in four or five days. This period of time is sufficient to enable the gel to reach equilibrium hydration and to extract any of the water soluble residual monomers present.

2.3.2 Skin Adhesive Membranes

Skin adhesive membranes are produced in a similar way to non adhesive membranes. However they require only one glass plate mounted with a melinex sheet and the

monomer mixture contains less photoinitiator and cross-linker than the fully hydrated, non-adhesive membranes.

To prepare a typical adhesive membrane, 5g of monomer mixture was mixed by a shaker to obtain a homogeneous solution to which 0.1% (w/w) of photoinitiator Irgacure 184 and cross-linker Ebacryl II mixture was added, in a ratio of 3:10 respectively. The solution was sonicated then poured onto the melinex mounted glass plate and subsequently placed under a medium intensity mercury lamp for approximately 20 minutes. The resultant gel was adhesive, and hence, if two glass plates had been used they might have adhered together and destroy the gel when separated. On completion of polymerisation the Melinex sheet was removed from the glass plate and the gel was stored until testing.

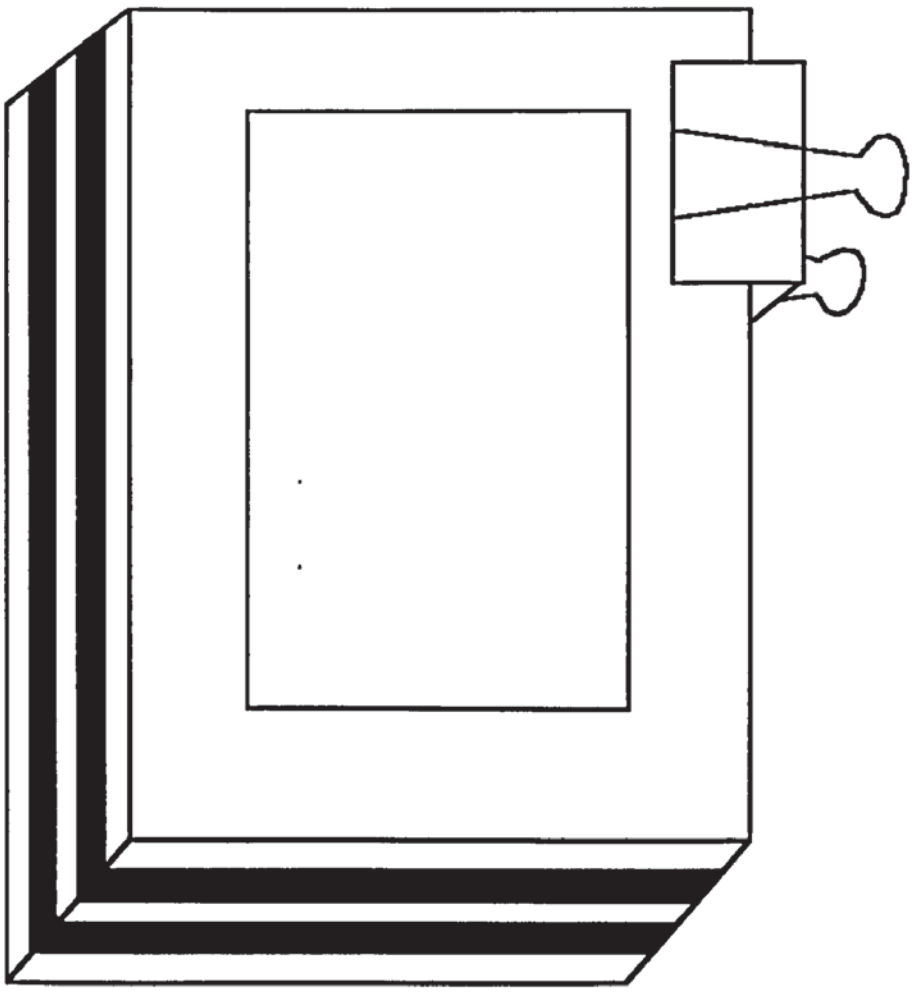


Figure 2.1 Two glass plates (15cm x 10cm) each surfaced with a "Melinex", [(polyethylene terephthalate)] sheet.

2.4 Photopolymerisation of Monomer Mixture

The monomer mixture containing cross-linkable monomers and a photoinitiator (Irgacure 184) are placed under a medium intensity mercury lamp either between or on glass plates. The mixture forms a cross-linked product in approximately 20 minutes, the length of curing time changes with the different monomer solutions and photoinitiator quantity used. Alternatively the monomer mixture can be poured onto a tray and passed under a UV lamp system with an automated table. This system cures the gels after approximately 7 passes and allows larger gels to be produced for more accurate testing.

2.5 Measurement of Equilibrium Water Content

When hydrophilic cross-linked polymers are placed in water or biological fluids they will swell, imbibing fluid until an equilibrium is reached between the fluid uptake and the physical restrictions of the three dimensional polymer network. The fluid absorbed by the polymer is quantitatively represented by the equilibrium water content, EWC. The EWC is the ratio of weight of water in the hydrogel to the weight of the hydrogel alone at equilibrium hydration, expressed as a percentage. It is an important factor in determining properties of the gel such as interfacial tension, permeability and skin adhesion. The EWC is influenced by the nature of the monomers and cross-linker used, the cross-link density, the tonicity of the hydrating solution and the temperature and pH of the system.

To determine the EWC, samples of hydrogel were soaked in distilled water and the latter changed daily for one week. The hydrated samples were cut using a size 7 core borer (12.5mm), blotted with filter paper to remove surface water and weighed on an electronic balance prior to dehydration in a microwave set to medium high power for ten minutes. The dehydrated samples were immediately re-weighed and the EWC was calculated using the formula:

$$EWC = \frac{[(\text{Wet weight}) - (\text{Dry weight})]}{(\text{Wet weight})} \times 100$$

Equation 2.1

In order to achieve a degree of accuracy of ±1%, the EWC value was measured for 6 samples with the assumption that upon dehydration no water remains within the sample and blotting prior to weighing removes only the surface water[67]. The result shown is an average value of the 6 readings recorded. More sensitive techniques exist to determine the EWC in hydrogels such as the Karl Fischer Titration[68]. This technique has been used previously to confirm the validity of the gravimetric technique described above.

2.6 Tensile Strength Testing

The mechanical properties of the hydrogels under tension were investigated using a Hounsfield Hti tensometer, interfaced to an IBM 55SX computer. The tensometer was fitted with a 10N load cell which was attached to the instrument's cross-head which moved in a vertical direction. Values for a set of parameters were entered into the program to control the cross-head speed and to allow the calculation of specific properties for the sample under test. The cross-head was raised at the selected speed until the sample broke completely.

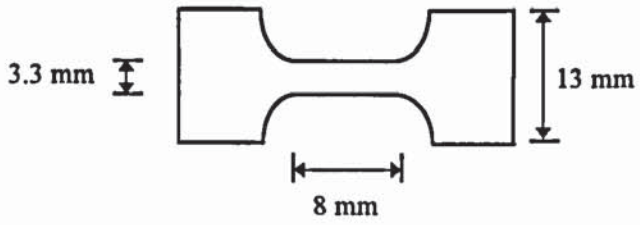


Figure 2.2 Dumb-bell shaped specimens of hydrogel sample.

Dumb-bell shaped specimens of gauge length 8 mm and width 3.3 mm were cut from the hydrated sample being tested. These test specimens were then equilibrated in distilled water to ensure complete hydration prior to clamping between the rubber coated jaws of the tensometer. A micrometer was used to measure the thickness of each sample before being placed in the jaws of the tensiometer. The mechanical testing of hydrated specimens of this type presents problems because the swollen hydrogels can be extremely weak and hence, can exhibit poor mechanical strength. This weakness and the requirement that the sample does not de-swell during testing requires the adoption of unique measurement procedures. Such problems are overcome using a standard test

method in which a fine spray is used to ensure complete hydration during testing. The samples were tested to break at an extension rate of 20 mm/min. The software calculated tensile strength at break (Ts), elongation at break (Eb) and Youngs modulus (E) of the sample under test. In addition, it enabled load/elongation curves to be plotted and performed a statistical analysis of the test runs on each sample[10,69] . To accomplish this the following equations were used:

$$\text{Young's modulus (E)} = \frac{\text{stress}}{\text{strain}} \qquad \text{Equation 2.2}$$

where

$$\text{stress } (\varepsilon) = \frac{\text{load}}{\text{cross-sectional area}} \qquad \text{Equation 2.3}$$

and

$$\text{strain (e)} = \frac{\text{extension of gauge length}}{\text{original gauge length}} \qquad \text{Equation 2.4}$$

$$\text{Tensile strength } (\sigma_b) = \frac{\text{load at break}}{\text{cross-sectional area}} \qquad \text{Equation 2.5}$$

$$\text{Elongation at break (Eb)} = \frac{\text{extension of gauge length}}{\text{original gauge length}} \times 100 \qquad \text{Equation 2.6}$$

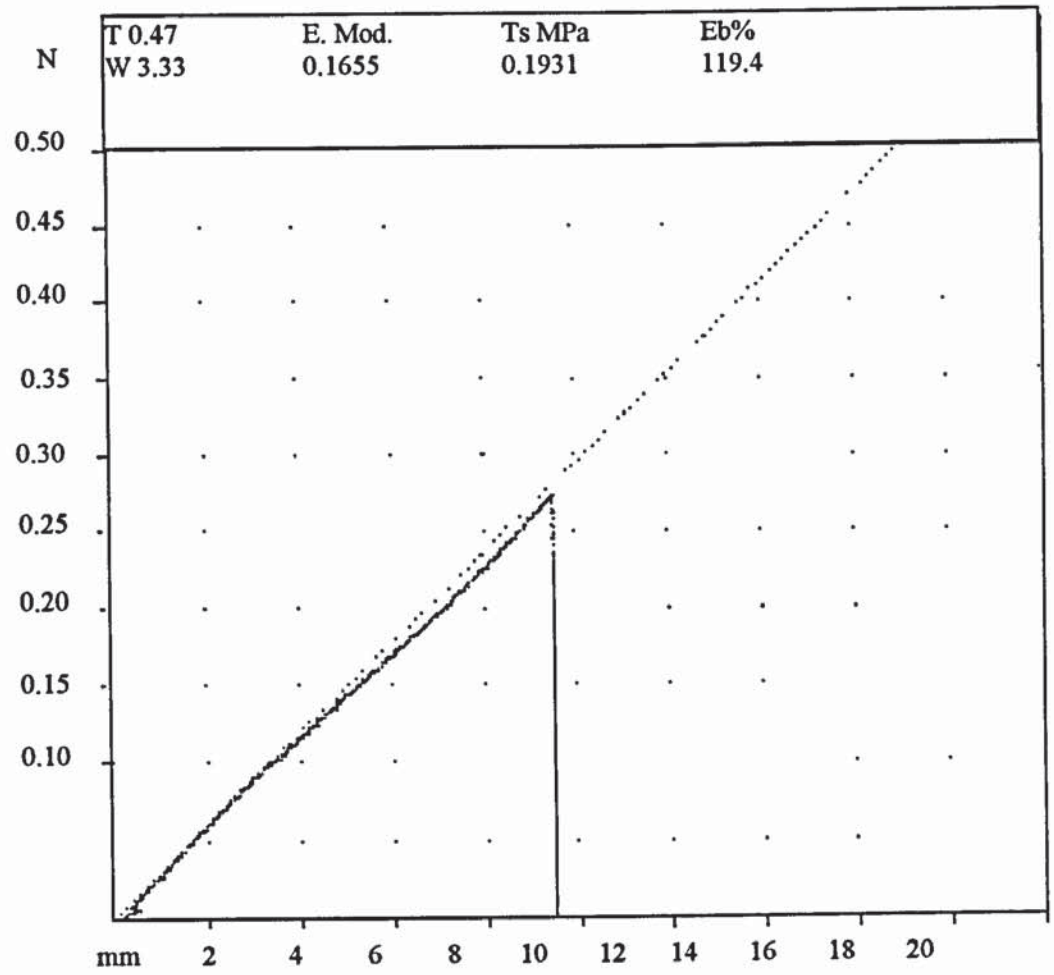


Figure 2.3 An example of a stress-strain curve obtained from the tensometer.

2.7. Differential Scanning Calorimetery

A Perkin Elmer differential scanning calorimetery, DSC 7 fitted with a liquid nitrogen subambient accessory was used to obtain thermograms. Hydrated samples were cut with a size 1 core borer (4mm) and blotted prior to being weighed and sealed in aluminium pans. The pans were placed in the DSC and cooled to -70°C to ensure the freezing of any supercooled water. The samples (approximately 6mg) were heated to -25 °C at a rate of 20°C min^{-1} and subsequently heated to room temperature at a rate of 10°C min^{-1} to produce separated endotherm peaks in the region of the melting point of water, usually between -25°C and 10°C. The area under the resulting endotherm represents the energy required to melt the frozen water in the sample. The weight of the sample is known and the energy required to melt 1g of pure water is known. Therefore the percent of freezing water within the sample can be calculated using Equation 2.7. The sample is cycled three times to give more accurate results. Additionally a second sample from the same gel is used to ensure the first sample was not taken from an atypical part of the gel. This technique is typical for measuring the percentage of freezing water in a sample[70-74]

$$\text{Freezing water \%} = \frac{\text{Energy required to melt water in 1g of sample}}{\text{Energy required to melt 1g of pure water}} \times 100$$

Equation 2.7

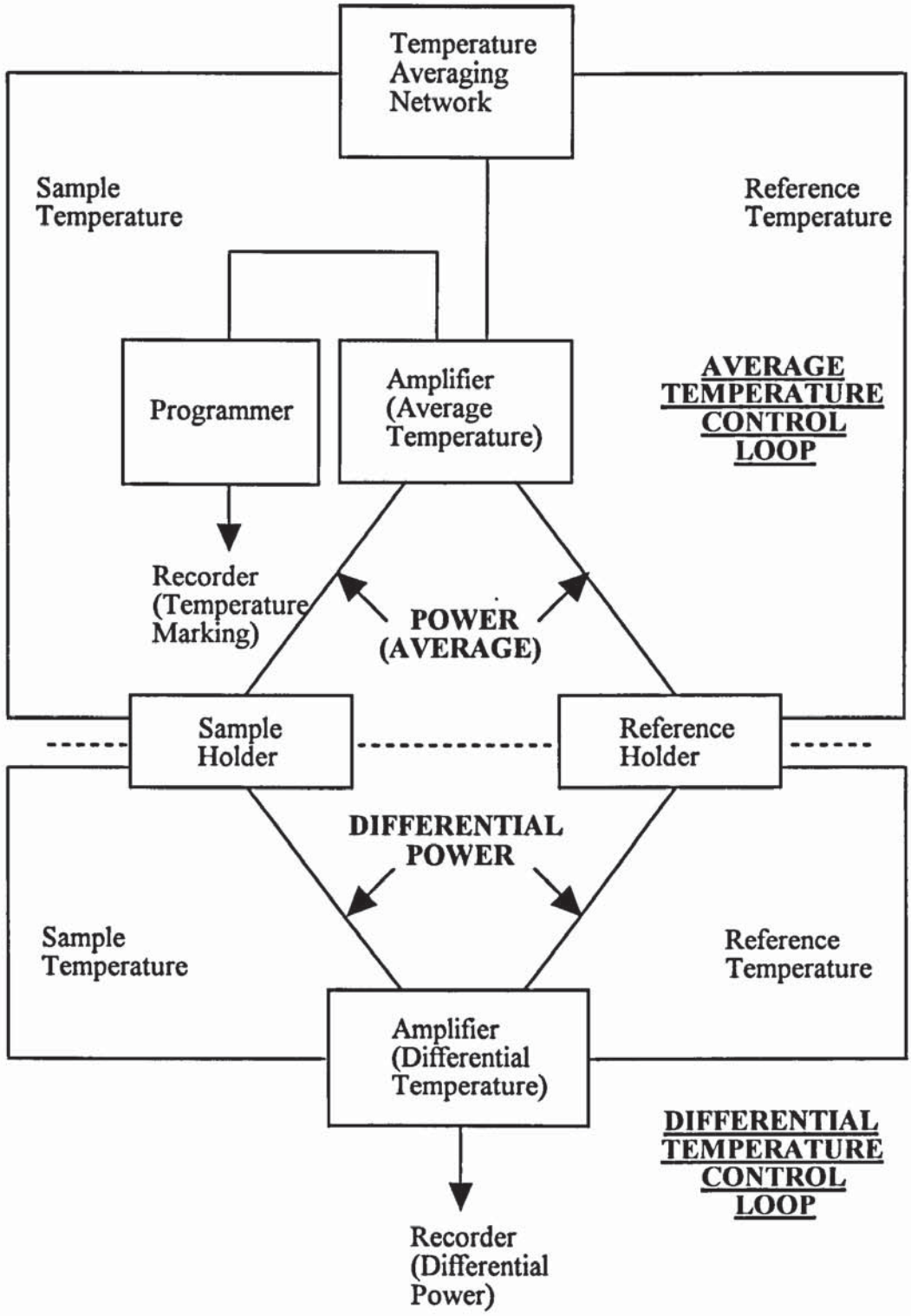


Figure 2.4 Schematic representation of a differential scanning calorimeter (DSC).

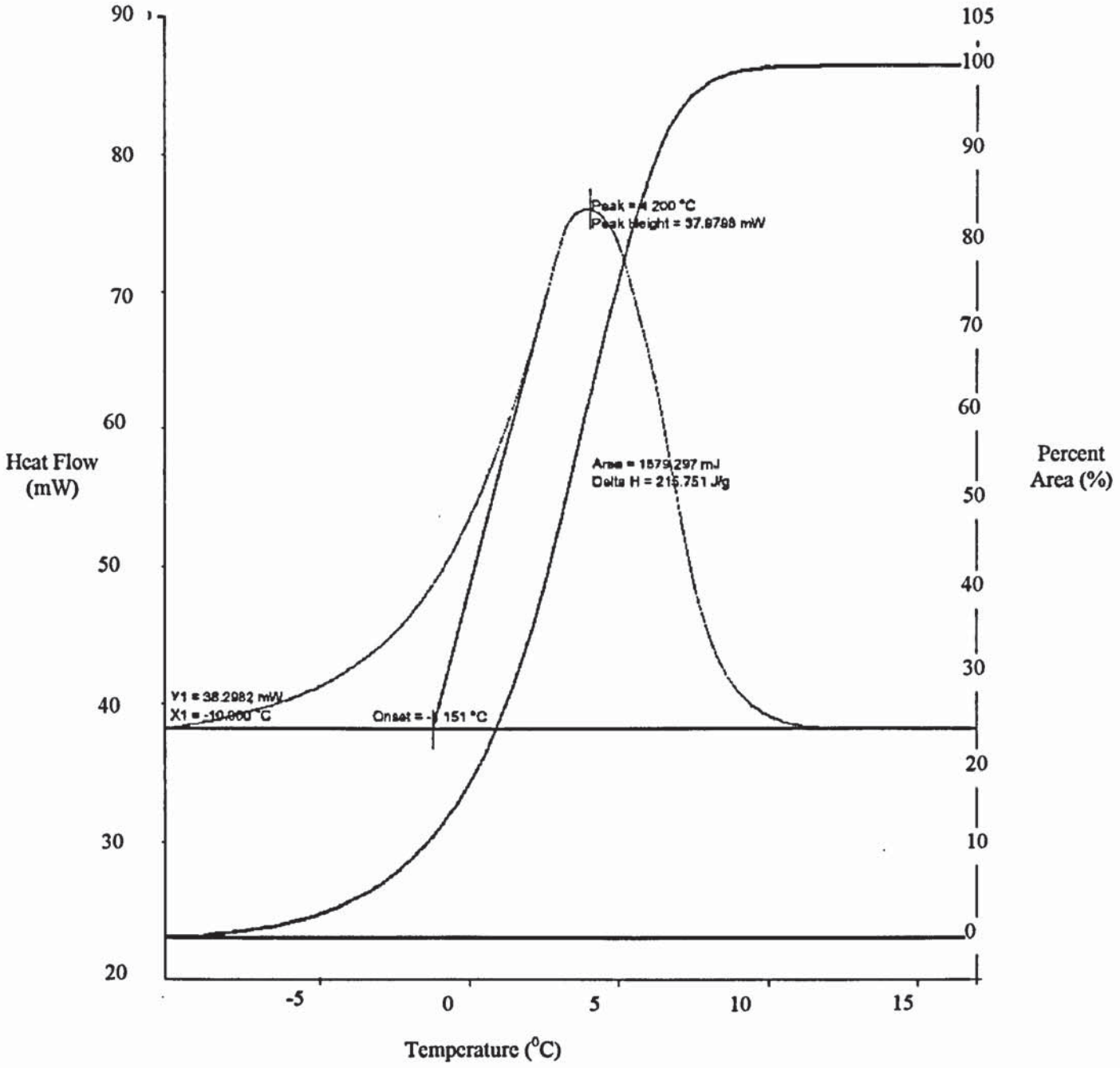


Figure 2.5 This diagram shows an example of a trace obtained from the DSC where the area under the peak represents the amount of freezing water present in the sample.

2.8 Dynamic Vapour Sorption (DVS)

The DVS (Scientific & Medical) can be used for many functions such as determining heats of sorption and de-sorption and hysteresis due to sorption and de-sorption. In this study it was used primarily to determine the EWC of skin adhesive gels.

The DVS contains two sample chambers, one which serves as a reference, containing only a sample pan, the other containing a similar sample pan supporting the material to be investigated. A small sample of hydrogel, less than 100 micrograms is cut and placed delicately in the pan of the chamber. Both sample pans are connected to an extremely sensitive Cahn microbalance located within a sealed glass unit. The mass of the hydrogel is then recorded. This system is exposed to a continuous flow of air with a predetermined and constant relative humidity. The humidity is set to a level close to the gel's EWC. The humid air causes a constant moisture concentration and relative humidity to be established around the sample zone. This zone enables the rapid establishment of water vapour sorption or desorption equilibrium by maximising the mass transport of water vapour into and out of the material. This is achieved by mixing a stream of dry air with a stream of air at 100% relative humidity at a specific ratio in order to obtain the desired humidity level. If the gel is losing weight then it must be losing water and so the stream of 100% relative humidity is increased, if the gel is gaining weight then the flow of dry air is increased. When the gel weight becomes stable then the gel must be at its correct water content.

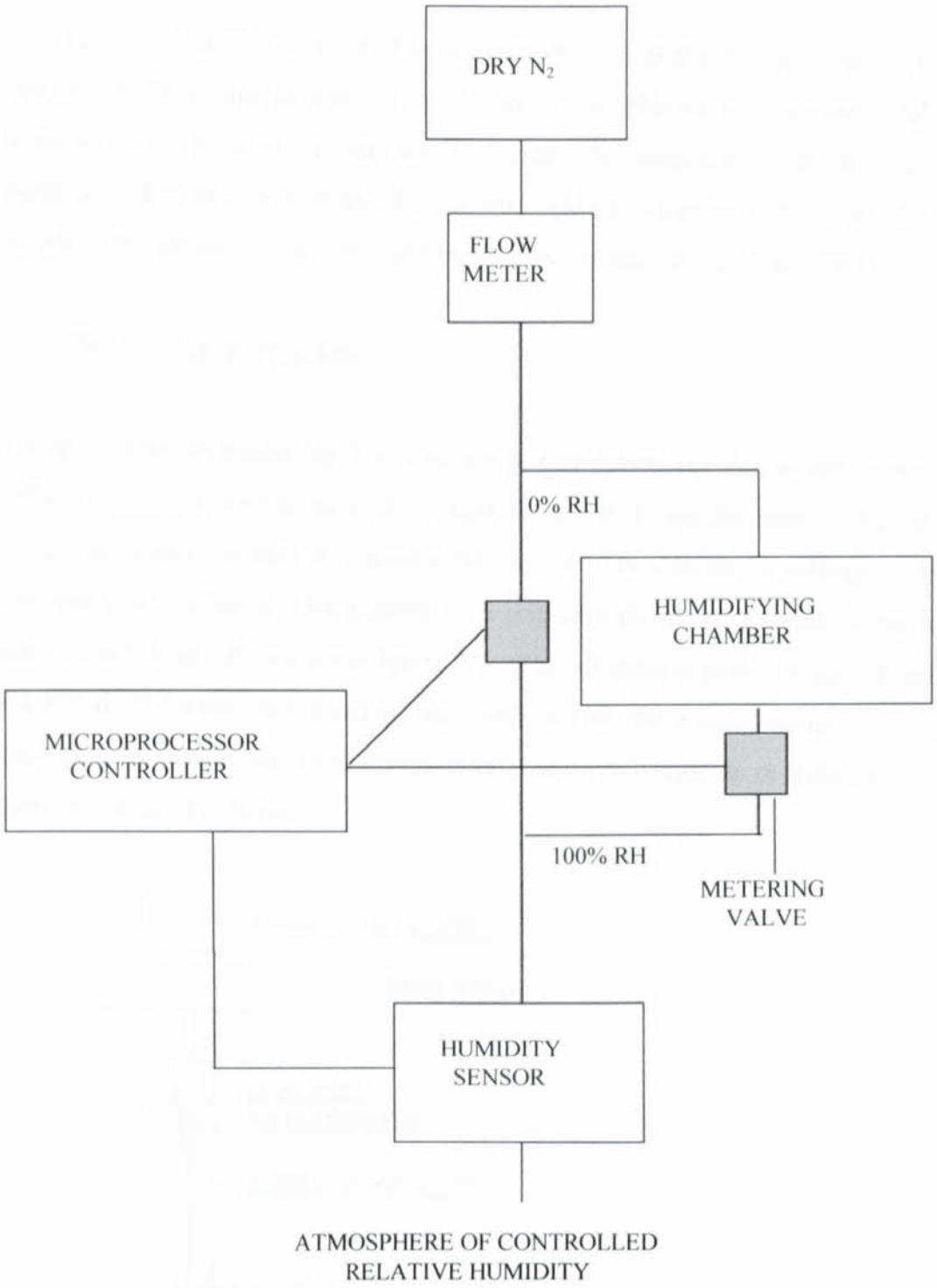


Figure 2.6 Schematic diagram of DVS flow stream of controlled humidity.

2.9 The Peel Test

Two types of peel tests were used to test the adhesion of the bioadhesives. They are the 180 and the 90 degree peel test. The backing of the adhesive is important. Melinex was found to be too rigid whilst foam was too weak. The underside of silicon coated release paper was ideal as it was strong, flexible and held the adhesive well. The solid support on which the adherend is adhered can be changed to suit the material tested.

2.9.1 The 180 Degree Peel Test

A strip of adhesive measuring 5 by 1 inch is placed against the skin model or skin, then a uniform pressure is applied by a 2kg weight being rolled over the adhesive backing. The skin model is securely held by a fixed solid surface. The adhesive is subsequently peeled from the solid surface at 180 degrees by a grip directly above the end of the adhesive using a 100N load cell, shown in figure 2.7. The adhesive is peeled from bottom to top at a speed of 500mm/min, bending back on itself as the peeling occurs. The grip is attached to a Hounsfield Tensiometer interfaced to a computer to determine the peel strength measured in N/mm.

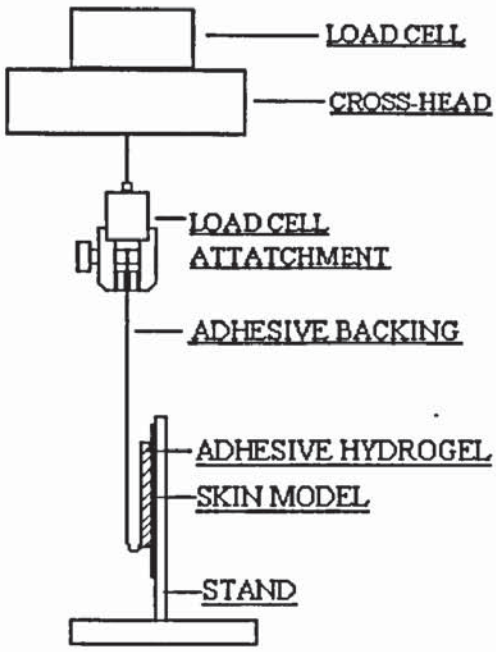


Figure 2.7 A diagrammatic representation of the 180 degree peel test adapted from a Hounsfield Hti Tensometer, interfaced to a IBM 55SX computer.

2.9.2 The 90 Degree Peel Test

The perpendicular peel test consists of a two wooden platforms, a base to support the testing and a plate which slides over the base. This plate enables the arm or material to remain in position whilst sliding over the base, allowing the angle of peel to remain constant at 90 degrees. This ensures the adhesive leaves the adherend directly below the peel grip. The 5 by 1 inch adhesive is pressed against the skin model by a 2kg weight being rolled over it and subsequently peeled from the skin or material by a grip directly above the end of the adhesive at a speed of 500mm/min using a 100N load cell. As in the 90 degree peel test, the grip of the Hounsfield Tensiometer relates the information to a computer which determines the peel strength in N/mm. The 90 degree peel test is illustrated in figure 2.8 and trace is shown in figure 2.9.

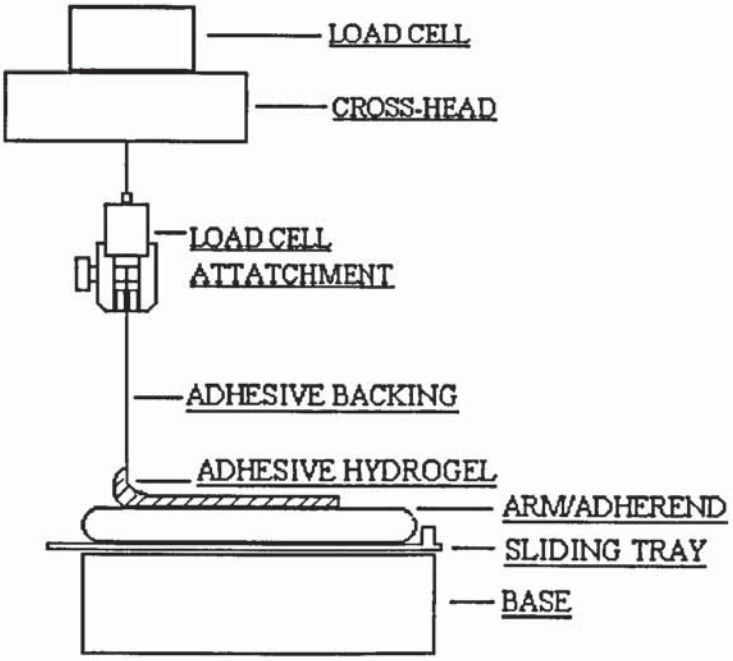


Figure 2.8 A diagrammatic representation of the 90 degree peel test adapted from a Hounsfield Hti Tensometer, interfaced to an IBM 55SX computer.

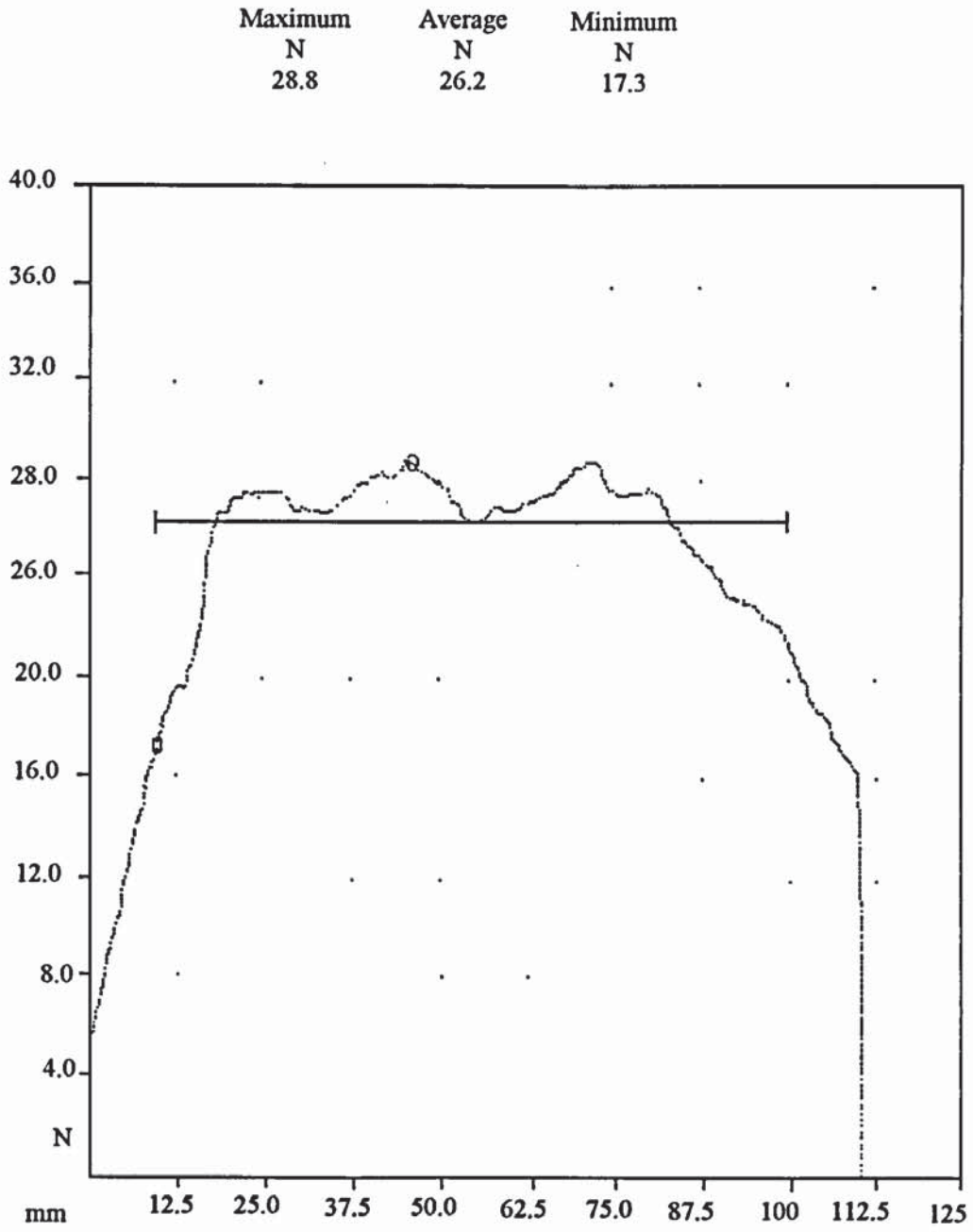


Figure 2.9 A trace obtained from a 90 degree peel test.

2.10 Contact Angle Measurements

The GBX Goniometer (shown in figure 2.10) can be used to measure the contact angles of liquid on a material instantly or over a period of time. The contact angle measurement is used to determine the polar and dispersive components of the hydrogel surface.

Two hydrogel samples of approximately 3cm by 1cm are cut and one is placed under a syringe containing water. Drops of water of a set volume, for example 2.5 µl are placed on the hydrogel and the angle of contact is measured from the image taken immediately after the drop has reached the hydrogel. The computer calculates the contact angle, thereby minimising human error. This is repeated several times to ensure the contact angle obtained is as accurate as possible and typical for the material being analysed. This process is repeated for another sample of the same material using diiodomethane instead of water. The contact angle using diiodomethane and water provides information to determine the dispersive and polar components respectively and hence the total surface free energy.

2.10.1 Kinetic Contact Angle Measurements

Kinetic measurements are performed in the same way as contact angle measurements except the contact angle of the drop is recorded a preselected number of times over a specified period, for example 40 measurements made over 80 seconds. This gives information on the interaction of the drop with the hydrogel over time.

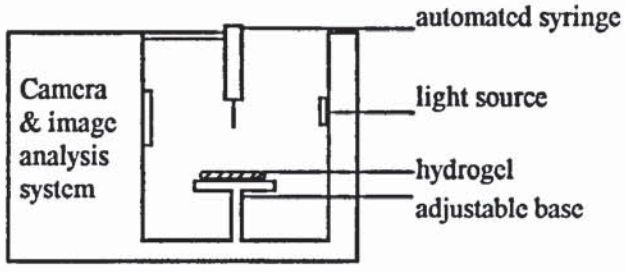


Figure 2.10 A diagrammatic representation of the GBX Goniometer.

2.11 Dynamic Mechanical Properties

Dynamic mechanical properties of hydrogel samples were tested on the Bohlin rheometer between 2 parallel plates (the base plate and an adjustable top plate). The two plates are brought together and the rheometer is zeroed to ensure that the rheometer plates are parallel and touching. The plates are subsequently set to 37 degrees Celsius (body temperature) for testing and allowed to reach that temperature. Circular discs of hydrogel approximately 25mm diameter and 2 mm depth are cut and placed between the 2 parallel plates. The top plate is brought into contact with the top of the gel. Any excess hydrogel protruding from the plates was trimmed off. Oscillation measurements between a frequency of 1-100 radians per second are recorded graphically.

2.12 Scanning Electron Microscopy

Scanning electron microscopy (SEM) is a non-invasive but destructive technique where samples, in this case pressure-sensitive adhesives, are viewed at very high magnification. Strips of various pressure-sensitive medical adhesive tapes were applied to the inner forearm of the subject. These were peeled off either immediately or after a specified period of time. For chosen adhesive tapes, subsequent peels of fresh tape were performed at the same site as previous peels. After each peel, small samples of the adhesive of approximately $5mm^2$ were placed adhesive side up onto scanning electron microscopy stubs and splutter coated with gold. The samples were then examined under a Cambridge Stereoscan S.E.M. with a X100-250 magnification at 25 kilovolts. In this technique, a beam of electrons is directed at the sample and the reflected electrons are collected and an image is displayed on a cathode ray tube. A thermal image of the adhesive surface is displayed on the cathode ray tube and recorded in the form of photographs.

For adhesive hydrogels the same procedure is repeated however the water in the hydrogel sample is removed by critical point drying using Freon liquid prior to gold plating[75].

2.13 Critical Point Drying of Hydrogels

Samples of hydrogels of approximately 5mm^2 were placed in baskets and filled to maximal capacity with Freon. The baskets were then placed in a critical point dryer and the chamber door closed. The carbon dioxide cylinder was then turned on, making sure outlets A and C were closed. The gas inlet B was opened and Freon was permitted to enter (making sure the pressure does not rise above 1200 P.S.I.) and closed when Freon had been observed to have reached the roof of the chamber. Outlet C was subsequently opened to release the pressure. This whole process was repeated 6 times. Hot water flow was then turned on to increase pressure. The temperature was required to reach 37 degrees Celsius at 1200 P.S.I. When the required temperature and pressure was reached the water flow was turned off and the samples were left for a couple of minutes. Outlets A and C were then opened. The critical point dried samples could now be removed from the chamber.

Figure 2.11 A diagrammatic representation of a Critical Point Dryer.

Chapter 3

Characterisation of Ionic Monomers

3.1 Introduction

As mentioned in the preceding chapters, the EWC is the single most important property of a hydrogel network and is governed by a range of factors which include the nature of the hydrophilic monomer used in preparing the gel, the nature and density of the cross-linking agent, and external factors such as temperature, tonicity (and nature) of the constituent ions and pH of the hydrating medium.

The water in a hydrogel plays a vital part in controlling the surface, mechanical and transport properties of the material which in turn govern its compatibility with the body. However, very different properties are required depending on the biomedical application involved.

Skin adhesive hydrogels, which may be employed as skin electrodes, transdermal drug delivery devices, biosensors and wound dressings, must have a high affinity for water (i.e. potential EWC). When applied to the skin they are only partially hydrated, but have a strong residual capacity to absorb interfacial water, thereby promoting adhesivity. A high work of adhesion is required for the gel to adhere to the skin, with careful control of surface chemistry being required to maximise interaction with the skin surface. The role of the polymer structure in controlling water binding is an essential element of the understanding and design of skin adhesive hydrogels.

These gels are not required to be transparent as most are covered with a backing. However, transparent gels are preferred for some applications as they are more acceptable to the patient or clinician. The gels must also have sufficient mechanical strength to enable them to remain cohesive should the gels require removal and repositioning. This is often achieved by the addition of a water swellable interpenetrant polymer. Skin adhesive electrodes and biosensors are required to be conductive and ionic monomers are often employed for this purpose (e.g., US patent 4,674,512., Rolf 1987)[26].

The aim of this chapter is to examine the nature and hydrophilicities of ionic monomers: the sulphopropyl ester of acrylic acid (SPA), the sulphopropyl ammonium betaine of

ethyl methacrylic acid (SPE), the sulphopropyl ester of itaconic acid (SPI), the sulphopropyl vinylpyridinium betaine (SPV) and sodium acrylamido methy propane sulfonic acid (NaAMPS). These were studied in the form of copolymers, together with a water soluble interpenetrant polymer, hydroxy propyl methyl cellulose (HPMC), water and glycerol.

The relative hydrophilic potential of the resultant gels were determined by fully hydrating them, even though they are only partially hydrated in their skin adhesive applications. The gels must be of acceptable quality with good mechanical properties, therefore ensuing investigations of different poly (ethylene glycol) dimethacrylates was performed to obtain strong, non-brittle gels. The gels were subsequently examined by differential scanning calorimetery to determine the percentage and states of water in the sample and furthermore mechanically tested to measure their strength.

3.2 Formulations for Membrane Production

A multi-component hydrogel based on semi-interpenetrating network technology is proposed to produce high water content membranes since this will allow sufficient flexibility of approach to optimise the final formulation to meet the detailed requirements of various processes and applications. In designing appropriate systems attention has been paid to the technology currently employed in conductive skin-contact hydrogels for clinical diagnostic instrumentation.

The separate components examined are:

[A] A water soluble interpenetrant polymer. This will provide a means of controlling the viscosity of the formulation to facilitate coating and also enhance the strength of the final gel. Possible candidates include: poly (vinyl alcohol), poly (vinyl pyrrolidone), poly (acrylic acid), poly (ethyleneglycol) or hydroxypropyl methyl cellulose (HPMC). HPMC has been chosen for initial experiments because it is available in a range of molecular weights that are characterised by their solution viscosity thus making modification of the viscosity of the final formulation simple. Poly (acrylic acid) and

polyethylene glycol should be examined as alternative, or even supplementary components.

[B] Functionalised polyethylene glycol (PEG), typically PEG dimethacrylate. In preliminary experiments PEG 600 and PEG 1000 dimethacrylates have been used where the number 600 or 1000 refers to the molecular weight of the functionalised PEG. The role of this component is to provide a photopolymerisable PEG network which can be augmented by other hydrophilic components. Alternatively PEG can be used as a mixture of PEG dimethacrylate and PEG monomethacrylate with appropriate adjustment of a conventional cross-linking agent (see [D]).

[C] An unsaturated water soluble hydrophilic monomer. Since conductivity of the final gel is important for some applications an ionic monomer in the form of the sodium or potassium salt has been selected. The selected monomers were the sulphopropyl esters of acrylic and itaconic acids, the sulphopropyl ammonium betains of ethyl methacrylic acid and the sulphopropyl vinyl pyridinium betaine. These monomers are supplied by Raschig as SPA, SPI, SPE and SPV respectively. The sodium acrylamido methyl propane sulfonic acid (NaAMPS) was supplied by First Water.

It may be possible to use one of a number of non-ionic monomers in the formulation as alternatives to the above. Acrylamide would be a logical choice if toxicity of the monomer were not an issue.

[D] A conventional cross-linking agent such as ethylene glycol dimethacrylate, di or tri-ethylene glycol dimethacrylate, methylene bis acrylamide etc. Methylene bis acrylamide was chosen. In the trial formulations the level of cross-linking was kept at around 1% in order to facilitate handling and testing of unsupported membranes. In the skin adhesive formulations it may be possible to reduce cross-linking with an anticipated gain in water content and reduced rigidity.

[E] Glycerol or a glycol. This serves to reduce the effects of evaporation of water from the finished formulation. In addition to their use in skin contact hydrogels, glycols have been extensively employed as diluents in the manufacture of hydrogels for

contact lenses, where their role in modulating the mechanical properties of the final network is believed to be important. Vistakon (a J&J company) have some pertinent patents that provide information without appearing to impinge on the use of glycols in the application considered here[76].

[F] Water. Although it is not uncommon to incorporate some water in the polymerisation mixture, it is usual to prepare hydrogels either in the absence of water, or with only a small amount. On placing the gel in water it swells to its equilibrium water content. In some applications, such as the one considered here, the aim is often to incorporate water at a higher level than the equilibrium swelling value. This usually modifies the pore structure of the gel and usually results in formation of an opalescent or even opaque material. This has not been considered to be a major issue here. Firstly, a modified pore structure will enhance permeability at lower water contents than might otherwise be acceptable. Secondly, with very thin (ca 100 micron) films low levels of opalescence will not be detected. Levels of water can only be meaningfully adjusted in the final formulation.

[G] Added salts. This variable can be optimised in formulations designed for specific applications.

[H] A photoinitiator. Although compounds such as riboflavin are biologically acceptable their effectiveness does not match those of commercial systems. In view of the importance of curing schedule, attention was turned to commercial photoinitiators that are currently used in skin contact and ophthalmic hydrogels. Irgacure 184 appeared to be ideal for this application as it is non yellowing, produces relatively low odour and has absorption peaks in the range of 240-250 and 325-330nm.

Unsaturated water soluble hydrophilic ionic monomers in the form of the sodium or potassium salt were investigated to determine their characteristics. SPA has a sulphonate group which is expected to be a strong water binding group as well as a carbonyl group which will interact with water. SPI has two sulphonate groups and SPM has a methyl group on the double bonded carbon. NaAMPS has a sulphonate group and an amide group which are both important in water binding. SPP, SPE and SPV are all

zwitterions. SPE has a sulphonate group and quaternary nitrogen which is expected to bind water, in addition to a carbonyl group. SPP differs from SPE by an extra carbon and an amide group in place of the carbonyl group. SPV has a sulphonate group and a charged nitrogen in a pyridinium ring. All of these functional monomers have great water binding potential and were all investigated further.

3.3 Procedure to Produce Hydrogels

2.5% and 5% solutions of hydroxypropyl methyl cellulose were prepared in three solvents: (a) water, (b) water: glycerol [3: 1], and (c) water: glycerol [1: 1], These are referred to as solutions A and A'.

Mixtures of PEG200 dimethacrylate, PEG400 dimethacrylate, PEG600 dimethacrylate and PEG1000 dimethacrylate with the potassium salt of 3-sulphopropyl N,N dimethyl oxyethyl methacrylate (SPE) were made up in the following ratios: [9:1], [4:1], [3:2] and [2:3]. These are referred to as mixtures B, B', B'' AND B'''.

Individual mixtures A and B were then mixed in the ratios [35:65], [50:50] and [75:25]. To these mixtures were added 1% cross-linking agent (methylene bis acrylamide) and 1% photoinitiator (Irgacure 184).

The resulting compositions were injected into glass plate moulds and exposed to UV (medium pressure mercury) radiation in order to produce membranes for subsequent characterisation.

The photopolymerised membranes were removed from the moulds by separation of the plates. The membranes were subsequently hydrated in distilled water for 5 days minimum prior to determination of equilibrium water content and mechanical properties. The same procedure was repeated for the other ionic monomers, SPA, SPI, SPV and NaAMPS.

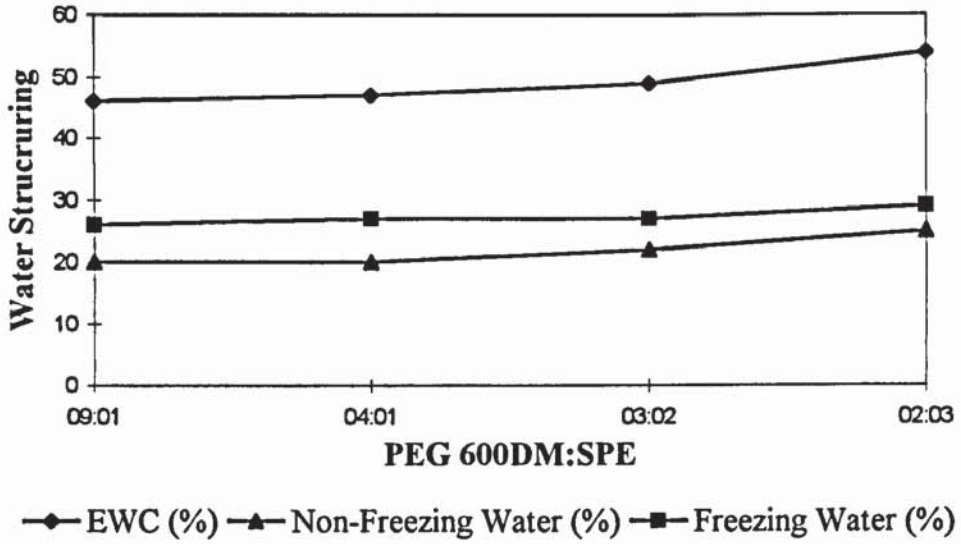


Figure 3.1 The water structuring for PEG 600DM and SPE at 35% liquid phase.

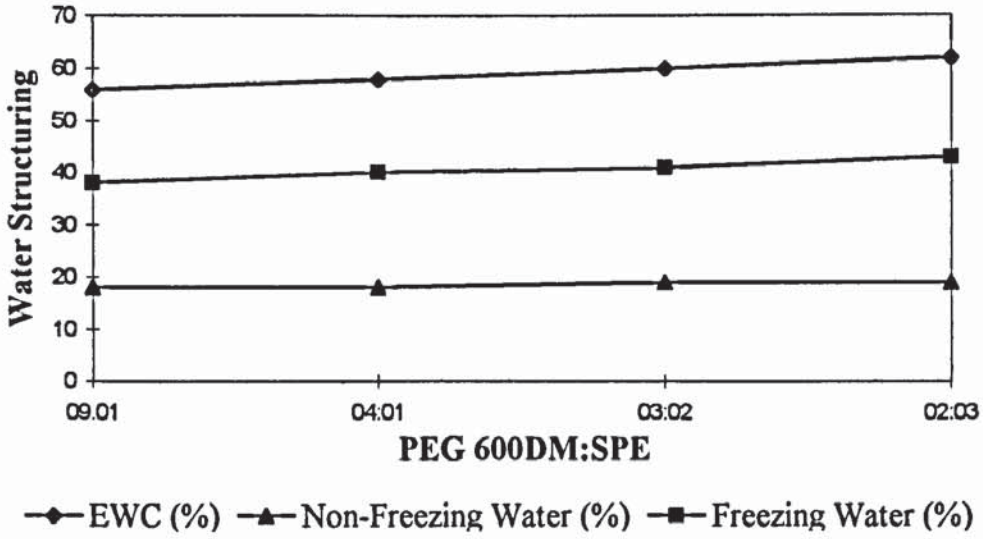


Figure 3.2 The water structuring for PEG 600DM and SPE at 50% liquid phase.

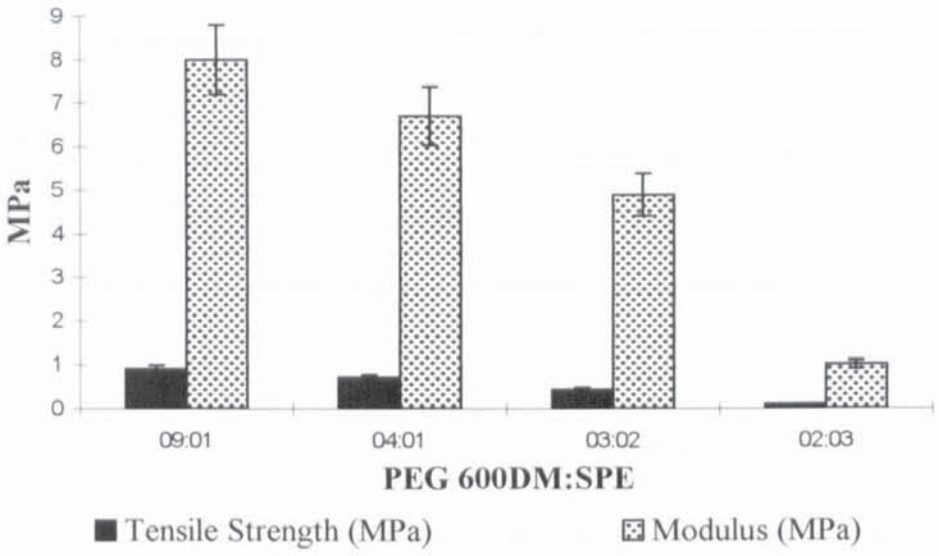


Figure 3.3 The tensile strength and modulus for PEG 600DM and SPE at 35% liquid phase.

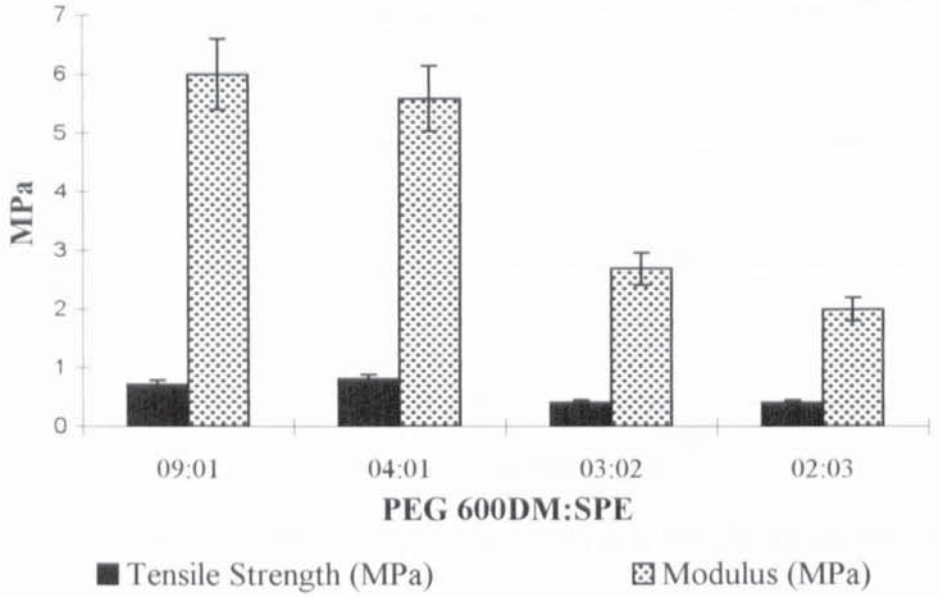


Figure 3.4 The tensile strength and modulus for PEG 600DM and SPE at 50 % liquid phase.

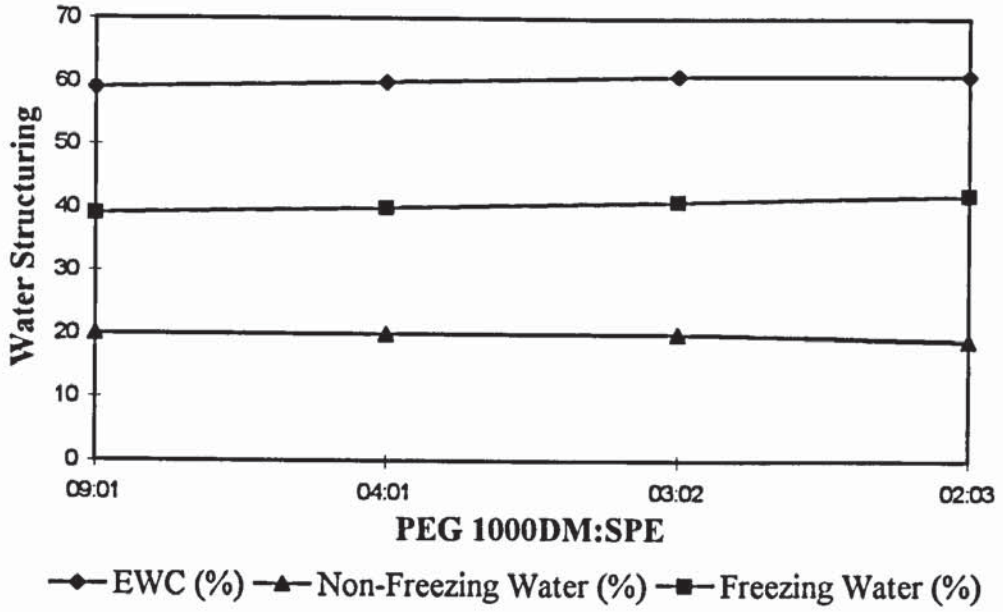


Figure 3.5 The water structuring for PEG 1000DM and SPE at 50% liquid phase.

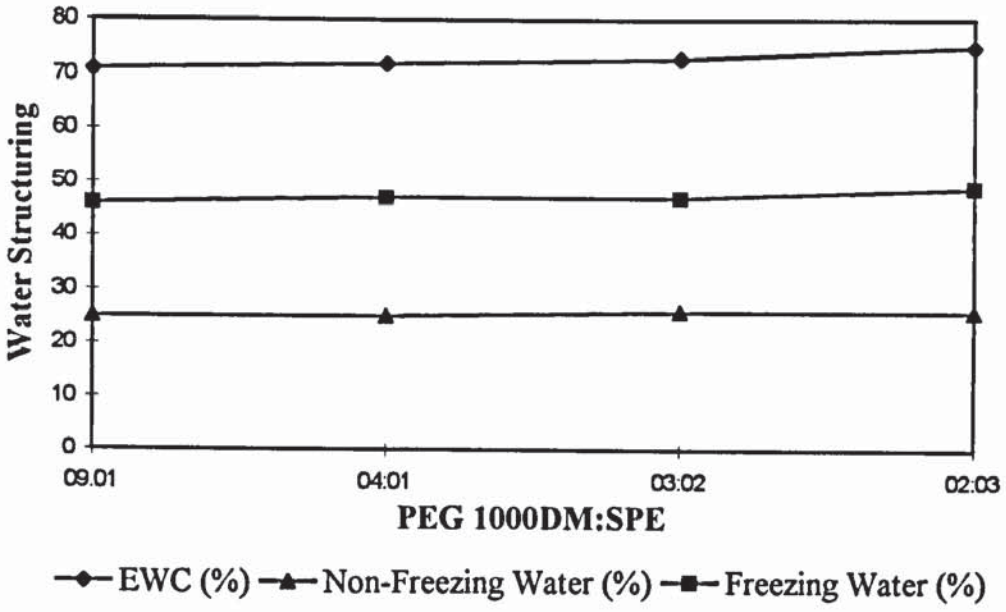


Figure 3.6 The water structuring for PEG 1000DM and SPE at 75% liquid phase.

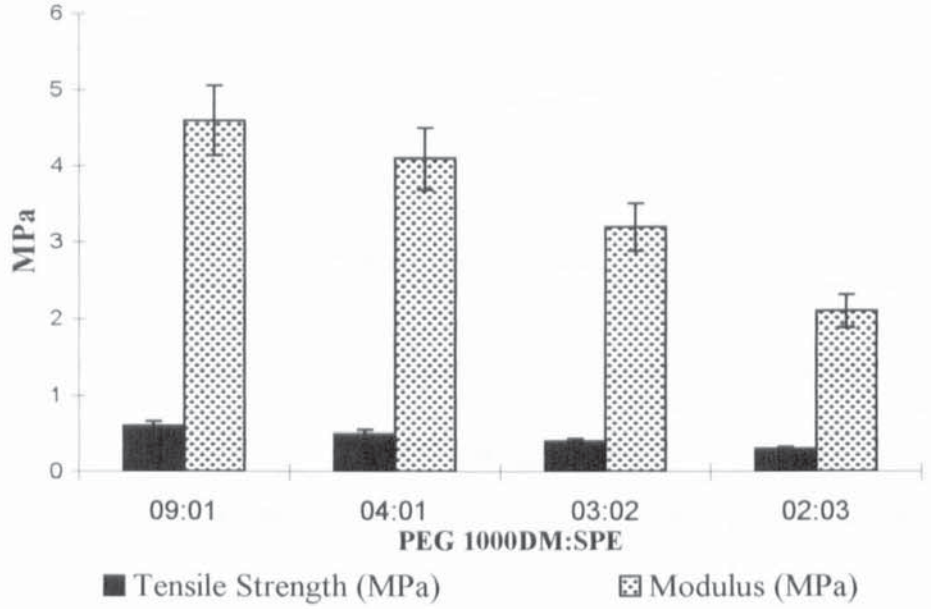


Figure 3.7 The tensile strength and modulus for PEG 1000DM and SPE at 50% liquid phase.

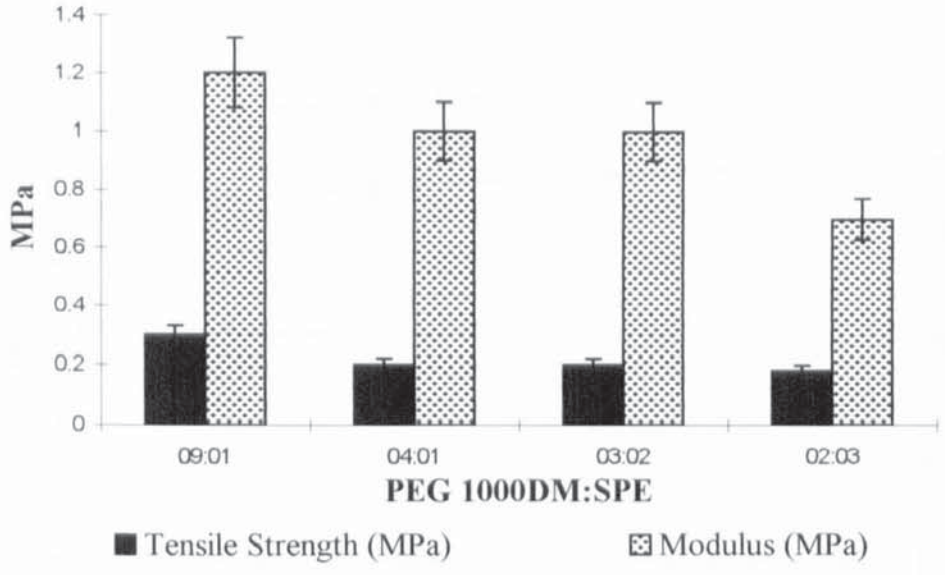


Figure 3.8 The tensile strength and modulus for PEG 1000DM and SPE at 75% liquid phase.

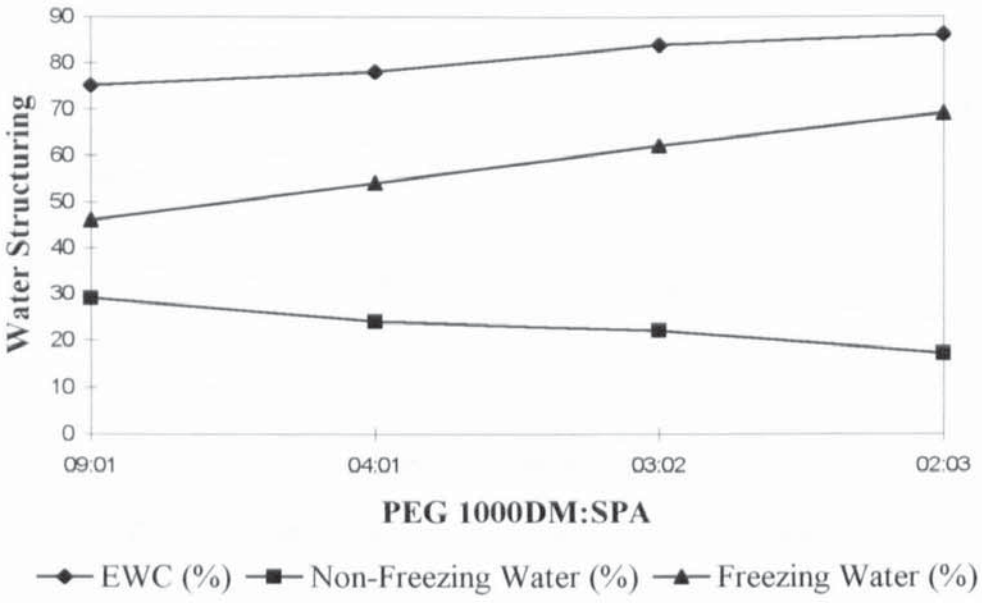


Figure 3.9 The water structuring for PEG 1000DM and SPA with a 75% liquid phase of water.

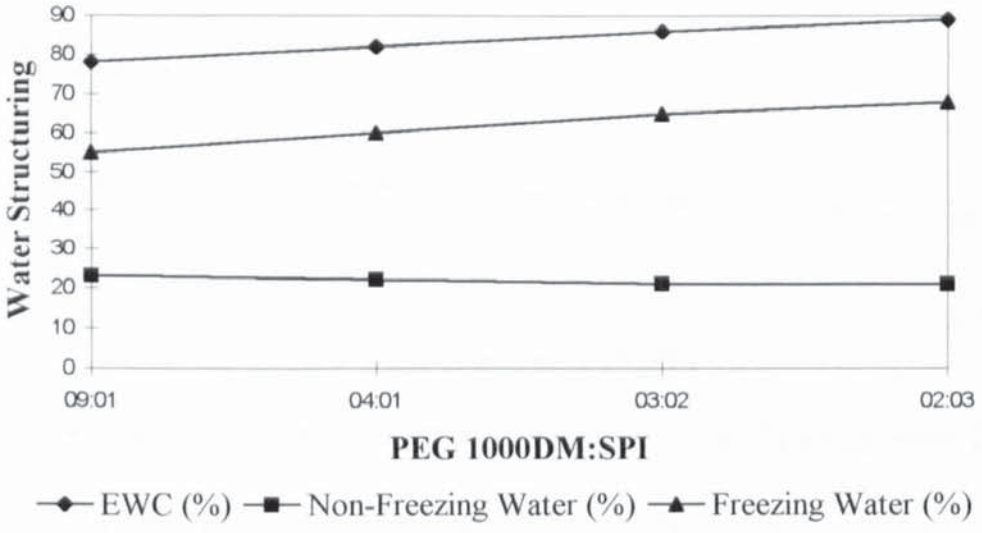


Figure 3.10 The water structuring for PEG 1000DM and SPI with a 75 % liquid phase of water.

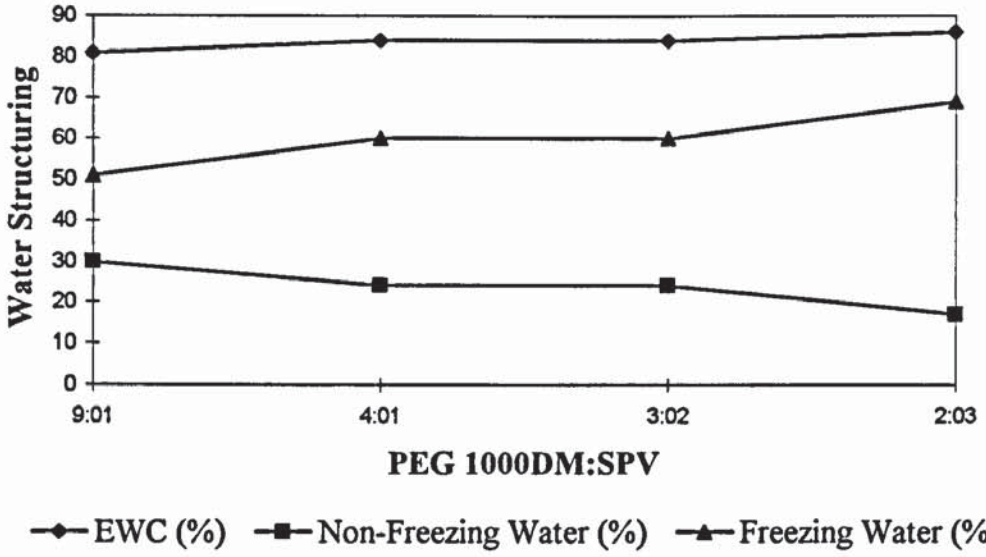


Figure 3.11 The water structuring for PEG 1000DM and SPV with a 75 % liquid phase of water.

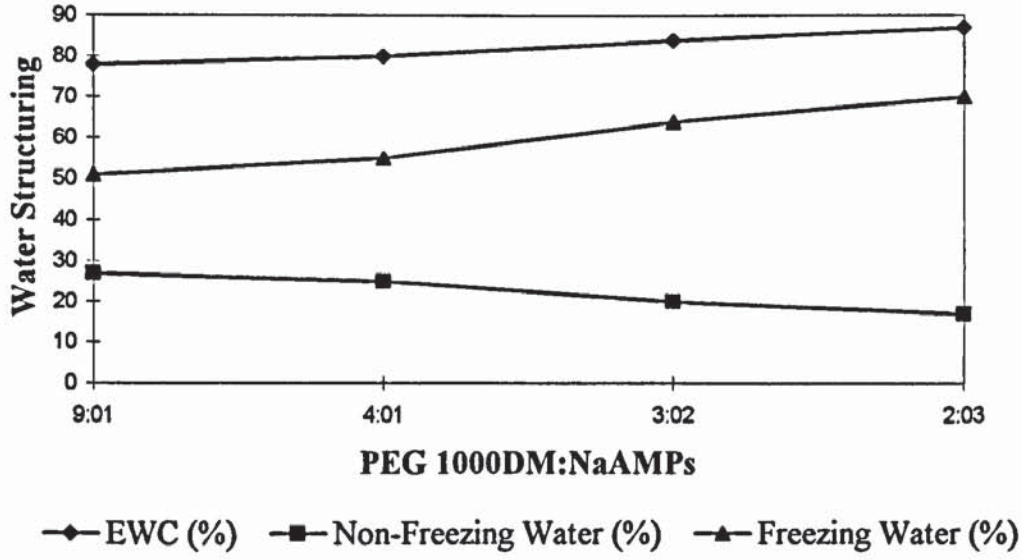


Figure 3.12 The water structuring for PEG 1000DM and NaAMPS with a 75 % liquid phase of water.

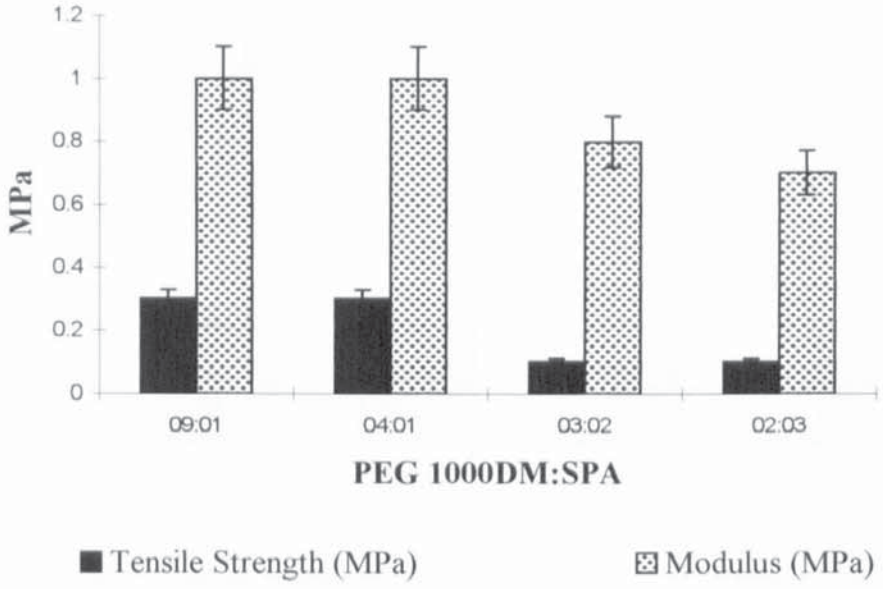


Figure 3.13 The tensile strength for PEG 1000DM and SPA at 75% liquid phase of water.

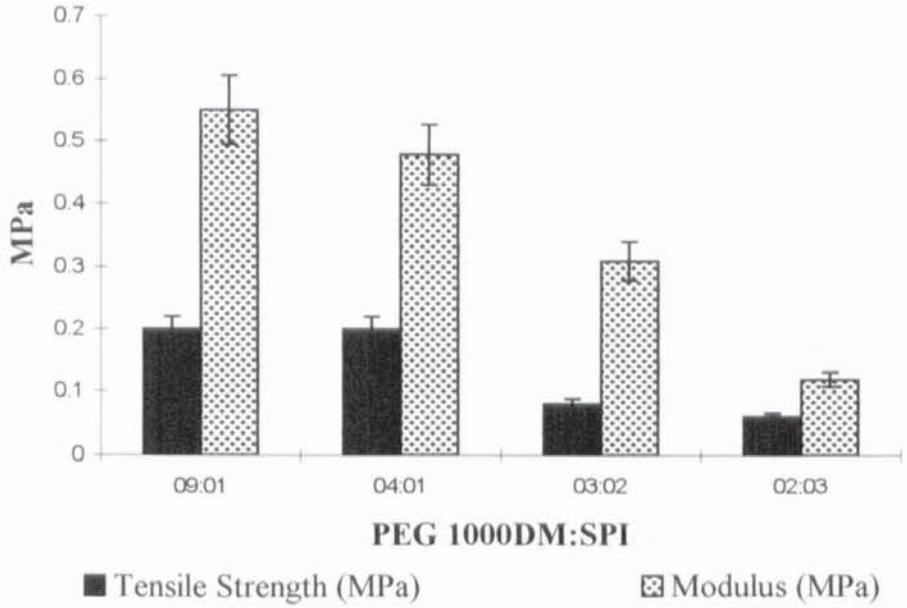


Figure 3.14 The tensile strength for PEG 1000DM and SPI at 75 % liquid phase of water.

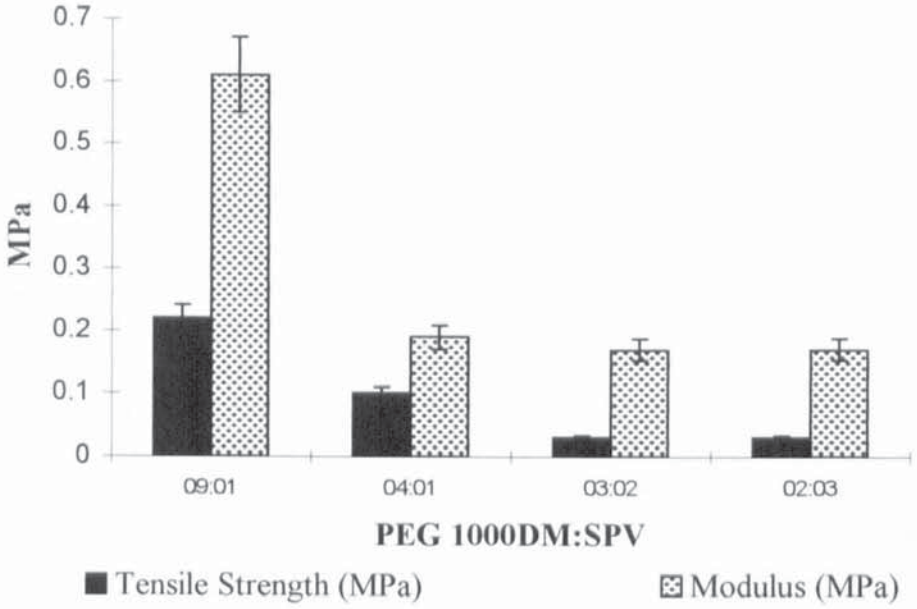


Figure 3.15 The tensile strength for PEG 1000DM and SPV at 75 % liquid phase of water.

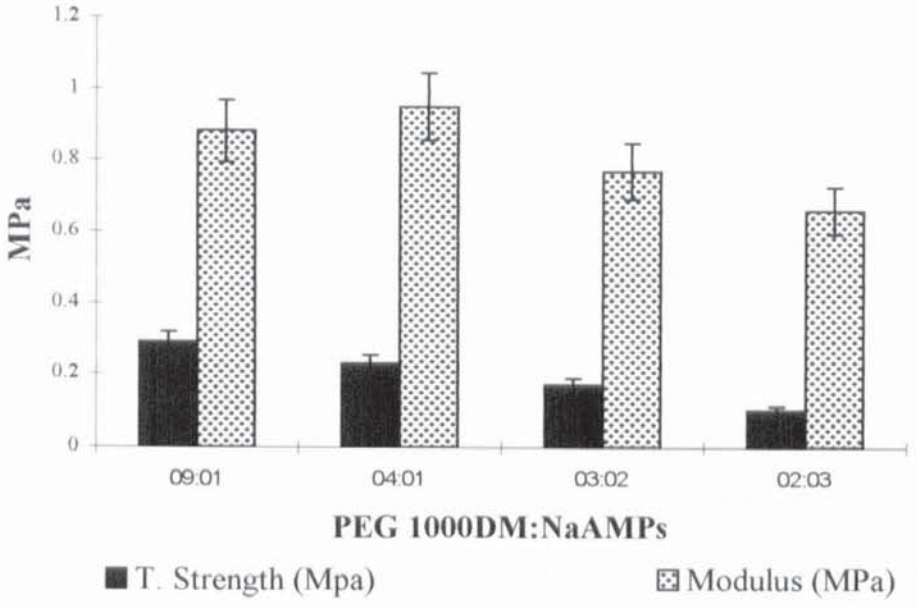


Figure 3.16 The tensile strength for PEG 1000DM and NaAMPS at 75 % liquid phase of water.

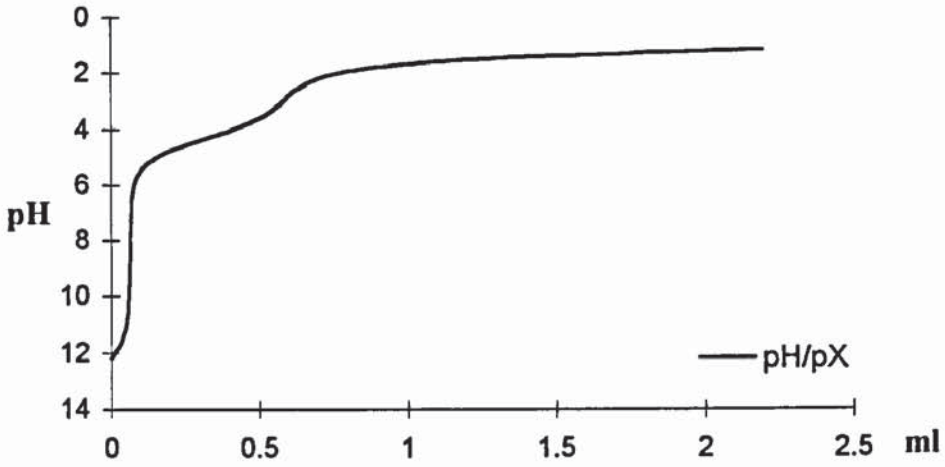


Figure 3.17 The titration curve for SPA.

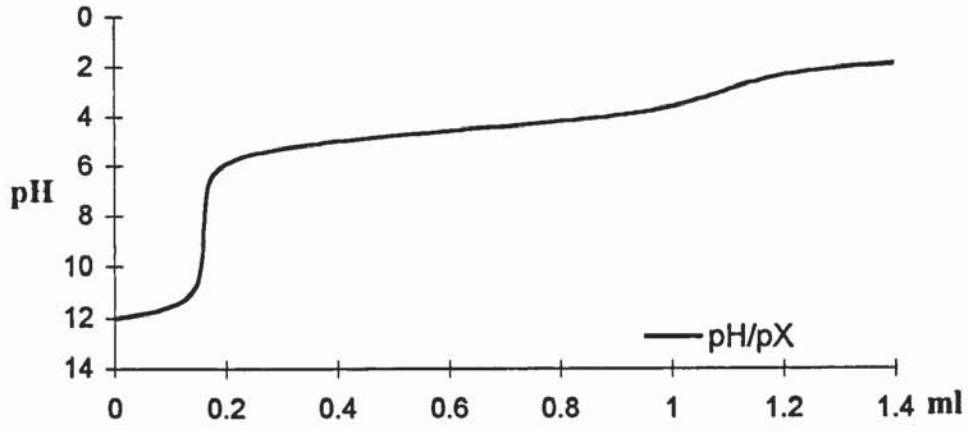


Figure 3.18 The titration curve for SPE.

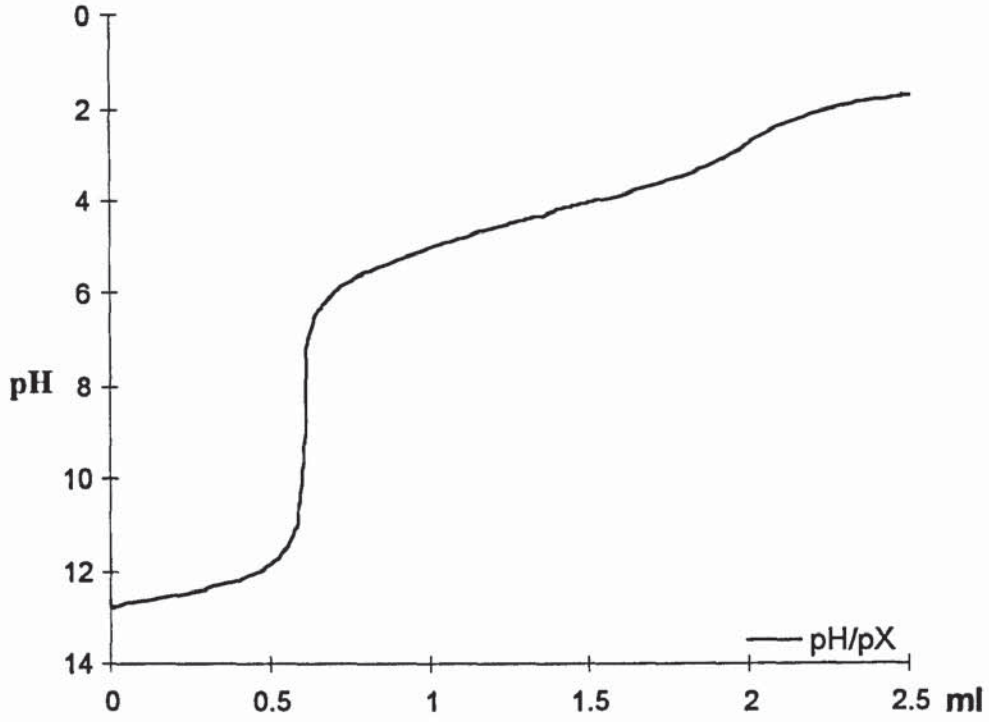


Figure 3.19 The titration curve for SPI.

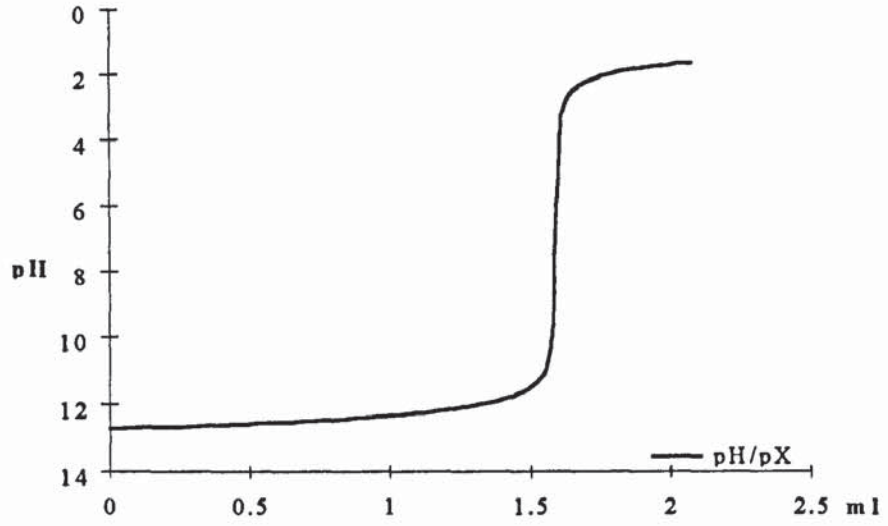


Figure 3.20 The titration curve for SPV.

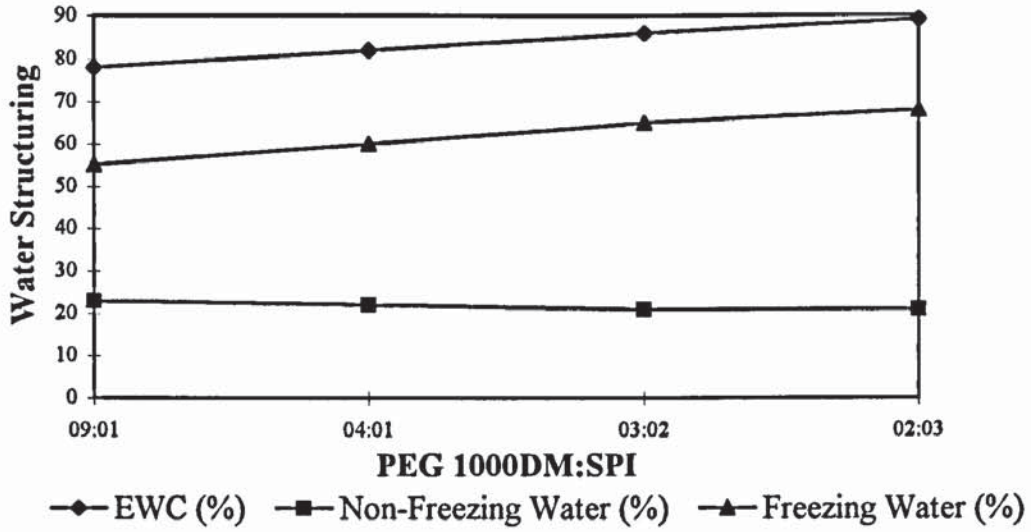


Figure 3.21 The water structuring for PEG 1000DM and SPI at 75 % liquid phase of water and glycerol [3:1].

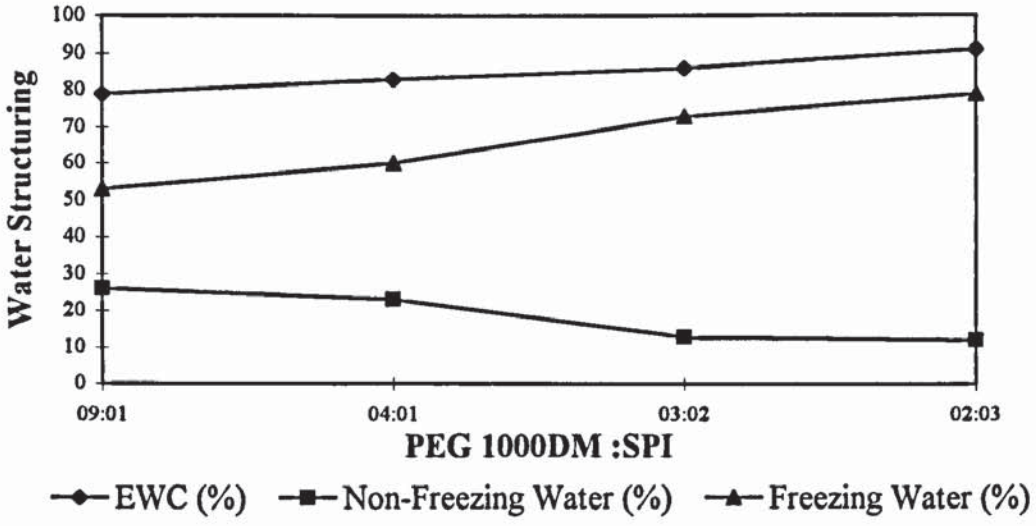


Figure 3.22 The water structuring for PEG 1000DM and SPI at 75 % liquid phase of water and glycerol [1:1].

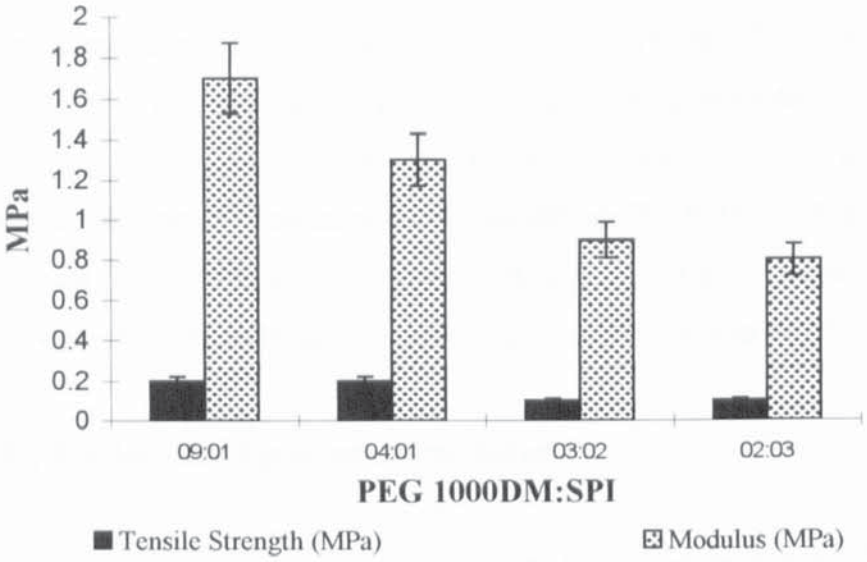


Figure 3.23 The tensile strength and modulus for PEG 1000DM and SPI at 75 % liquid phase of water and glycerol [3:1].

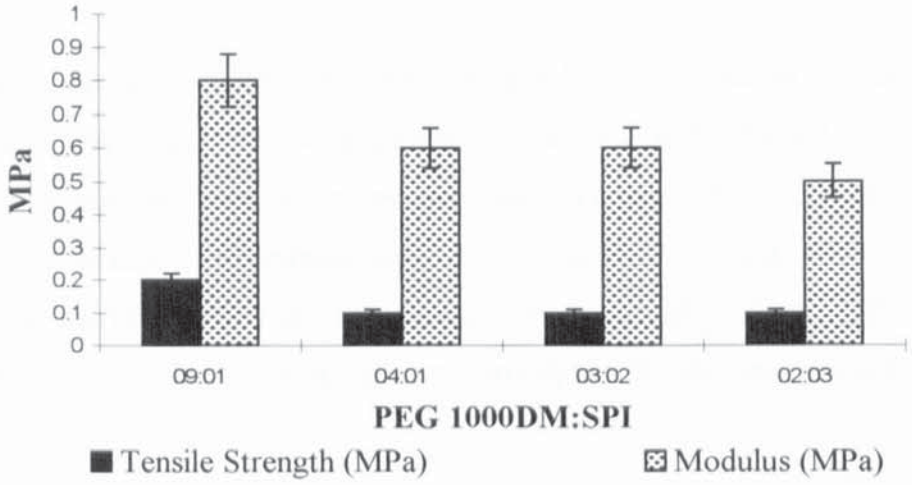


Figure 3.24 The tensile strength and modulus for PEG 1000DM and SPI at 75 % liquid phase of water and glycerol [1:1].

3.4 Solution Viscosity

It was difficult to produce bubble free membranes from the 5% HPMC solutions due to their viscosity. This is a consequence of the membrane plate technique and would not present a problem for coating or printing applications. The water contents and mechanical properties of membranes produced from 5% HPMC solutions were unreliable and are not displayed here. Solutions containing 2.5% HPMC were used as they do not exhibit excessive viscosity, can be manipulate and did not trap air bubbles.

3.5. Hydrophilic Photopolymerisable Networks

A range of PEG dimethacrylates were studied, they included PEG 200DM, PEG 400DM, PEG600DM and PEG1000DM. It was determined that the PEG200 and PEG400 dimethacrylates produced membranes that were too brittle for reliable testing because the effective cross-link densities increased as the length of the PEG block decrease, giving a high cross-link density resulting in inelastic, non-malleable gels.

Gels produced from PEG 600DM were the first good quality gels to be formed and tested. The results of these tests can be shown in figures 3.1 to 3.4. Figure 3.1 demonstrates the relationship between the EWC and ionic monomer SPE. At lower levels of incorporated aqueous liquid an increase in the ratio of SPE to PEG 600DM is seen to increase the water content, shown by the small increased EWC. At low liquid phase both freezing and non-freezing water appear to be contributing to this increase in EWC.

Figure 3.2 represents a series of gels consisting of the same components (appendix 1), differing only in the percent of liquid phase. This increase in liquid phase in the polymer mixture caused an increase in the EWC, due to an increase primarily in the ratio of freezing to non-freezing water content. This finding is familiar to all the ionic monomers used at higher liquid phase, confirmed by subsequent experiments with SPA, SPI, SPV and NaAMPS (figures 3.9-3.12).

The increase in EWC occurs at the expense of the tensile strength and moduli of the gels ,shown by figures 3.3 and 3.4. (appendix 1). Nevertheless, this is still acceptable as shown by comparison to the tensile strength and moduli of soft contact lenses, 0.2-0.5 MPa together with an elongation of 50 -100%, with water contents in the range 40 - 65%. It is clear from the results presented here that the materials with these combinations of water contents and cross-link density have adequate strength and stiffness. The elongations (which always exhibit an error range of +/- 30%) will rise and the stiffness (modulus) will fall as cross-link density is lowered.

PEG1000 dimethacrylate membranes were less brittle and more elastic than PEG600 dimethacrylate membranes. The decrease in the effective cross-link density enables a higher EWC to be attained, demonstrated by comparing figures 3.2 and 3.5, where again a slight decrease in moduli and tensile strength is observed (figures 3.4 and 3.7). As before when the liquid phase is increased, from 50% to 75%, the EWC increases , due to an increase in the ratio of freezing to non-freezing water (figures 3.5 and 3.6). This latter effect results in a reduced moduli and tensile strength as demonstrated in figures 3.7 and 3.8. However, all these values are still acceptable.

A high EWC is desirable and so PEG 1000 dimethacrylate was used for subsequent investigations as PEG DM of lower molecular weights gave too high a cross-link density which in turn reduced the EWC.. Alternatively, if desired, the cross-link density associated with PEG dimethacrylate could be reduced not only by increasing the PEG block size to 1000, but by using mixtures of PEG600 dimethacrylate (for example) with PEG monomethacrylate. The results clearly illustrate the importance of cross-link density. The retractive forces of the cross-links restrict water uptake and expansion, reduce flexibility and induce brittleness.

The cross-linker level remained constant throughout these experiments in order to facilitate comparison. The level was set at 1% to allow preparation of unsupported membranes yet this was rather high, indicated by the brittleness of the gel. The added cross-linking agent (component D) should be dramatically reduced, it may even be possible to eliminate it. A reduction in cross-linker will result in reduced cross-link density and increased water uptake.

The most effective way of increasing water content is to increase the liquid phase (amount of water or water plus glycerol) incorporated in the polymerisation mixture. When the liquid phase was increased further the resultant gels were weak and of poor tensile strength and moduli and gave unreliable results. Therefore 75% liquid phase was the highest liquid phase used.

3.6 Hydrophilic Monomers

The nature of the ionic hydrophilic group and its effective concentration in the monomer repeat unit both effect the hydrophilicity and specific water binding characteristics of the gel networks.

Comparison of the unsaturated, water-soluble, hydrophilic monomers showed that SPA, SPE, SPI, SPV and NaAMPS all have a high affinity for water (fig. 3.9-3.12 respectively) that is they imbibe a large volume of water. At equivalent weight percent incorporation, SPI was found to have the highest EWC, followed closely by SPA. SPE was found to have the lowest EWC at the same equivalent weight percent (fig. 3.6). In all cases the increase in EWC was due to an increase in the ratio of freezing to non-freezing water.

The effect of increasing the level of PEG DM or liquid phase was found to have the least with SPE, which additionally is the least hydrophilic monomer. The two effects are related in that the ionic interaction between the charged nitrogen and the sulphonate group within the monomer repeat unit produces both interchain and intrachain interaction serving to reduce the availability of water binding sites and to effectively act as the retractive force thereby countering hydration induced expansion of the network (fig.3.1, 3.2, 3.5 and 3.6). To this effect the presence of interchain ionic cross-linking within the monomer unit overwhelms the effect of covalent cross-linking at the levels used here. In the case of the other two monomers increasing cross-link density reduces network mobility and increases the ratio of non-freezing to freezing water.

When the sulphonate group does not have the opportunity to interact with the cationic nitrogen, as in the case of SPA and SPI shown in figures 3.9 and 3.10, it is extremely

hydrophilic. Arguably, there is no effective difference between the two dispositions of the sulphonate group found in SPA and SPI. The molecular weights are 232 and 450 respectively, which means that the molecular incorporation of sulphonate groups (i.e. moles sulphonate groups per unit mass of monomer) is nearly identical. The fact that SPI shows a slightly higher level of hydrophilicity is little more than a reflection of the small advantage that it has in this respect. The detailed water binding results of the sulphonate group in the three forms used here are also of relevance.

SPE, the least hydrophilic monomer with the lowest EWC, had the highest proportion of non-freezing water and lowest of freezing water. In the case of the SPA and SPI compositions studied here, as EWC increased, the non-freezing fraction of water decreased and the freezing fraction increased. This is illustrated for SPI in figure 3.10. The consequences of higher levels of freezing water (sometimes referred to as plasticizing water) include increased phase separation, pore size and permeability coupled with a decrease in optical clarity. This is generally associated with the increased light scattering as the size of water pores approaches the wavelength of light. The monomers SPA and SPI tend to produce clearer hydrogels, at equivalent weight for weight compositions due to more uniform hydrophilicity and the higher ratio of freezing to non-freezing water. Although some variations in the relative proportion of freezing and non-freezing water could be achieved at lower values of EWC, a comparison of all results show that this variation disappears as the gel takes in higher levels of water.

SPV, like SPE, is a true zwitterion, possessing both a positive and negative charge in the side chain. However, the ionic interaction between the charged nitrogen and the sulphonate groups on different repeat units must produce less of an interchain and intrachain interaction than in SPE and thereby present the water binding sites more effectively as it does not possess a similar water binding pattern. SPV displays a similar water binding tendency that is more similar to SPA and SPI and has a molecular weight of 227 giving it a similar molecular incorporation of sulphonate groups to both SPA and SPI (molecular weight 232 and 450 respectively). SPV was investigated primarily because it possessed a pK_a value around 6.5-7 which differed from SPA, SPE and SPI which all possessed pK_a values of 3 and pK_b values of 9 (fig. 3.17-3.20). The relevance of this is that skin has a pH around 5.5 which is in close proximity to that of the Pk_a

value of SPV which may enable SPV to be tolerated better by the skin.

NaAMPS is an ionic monomer used by First Water, a company who manufacture skin adhesive hydrogels to adhere electrodes to the body. This monomer was used to compare the hydrophilicity and specific water binding characteristics of the gel networks it produced with SPA, SPE, SPI and SPV. Figures 3.9-3.12 reveal that while NaAMPS boasts a similar water structuring pattern as SPA, SPI and SPV, for the same moles of sulphonate groups per unit mass of monomer (229 molecular weight), it has a slightly lower EWC which is unexpected considering its wide use in the skin adhesive areas.

For all gels, the greater the liquid phase, the greater the EWC. When water is used as the liquid phase the increase in EWC results in a decrease in tensile strength and modulus. Three solutions were used for the liquid phases; water, water and glycerol [3:1] and water and glycerol [1:1], shown by figures 3.10, 3.21 and 3.22 respectively. The gels produced with a liquid phase containing glycerol had a higher modulus and tensile strength than those produced with a liquid phase consisting of water alone, figures 3.14, 3.23 and 3.24. They also had a slightly higher EWC. The series of gels containing a liquid phase of equal glycerol and water content [1:1] had a higher EWC but lower tensile strength and modulus than the gels containing a liquid phase of water and glycerol [3:1].

3.7 Conclusion

The results show that three contributing factors have an effect on the hydrophilicity and specific water binding characteristics of the gel networks tested. The first factor is the level of high molecular weight hydrophilic cross-linking agent (PEG DM), PEG 1000DM was found to be the best as it produced non-brittle gels with high EWC. The second is the nature of the ionic hydrophilic group, in this instance the sulphonate groups of SPI and SPA appeared to make them the most hydrophilic and the third is the effective concentration of the ionic hydrophilic group in the monomer repeat unit. All ionic monomers had a similar molecular incorporation of sulphonate groups, with SPI having a slight advantage over SPA because it has a marginally higher ratio of moles of sulphonate groups per unit mass of monomer for the same number of ionic hydrophilic

groups.

The good hydrophilicity of SPI per unit mass renders it an obvious choice for use in bioadhesive hydrogels. Since the high affinity that the gel has for water enhances removal of moisture, reducing lubrication therefore presenting an adhesive surface which adheres to the skin. The large volume of freezing water is desirable for conduction as electrolytes are solvated within the aqueous portion of the polymer layer.

To make a functioning skin adhesive from these gels, the water content is reduced to around 30% and the ionic monomer, SPI, is increased to elevate the gel's affinity for water. The glycerol content is also increased as it reduces evaporation, and the cross-link level reduced to produce compliance. Ionic monomer, glycerol and water are the major components of many adhesive gels described in the patent literature.

Chapter 4

Adhesive Gels

4.1 Introduction

A basic series of components commonly used to make bioadhesives were examined to determine their effects on adhesion. The components used are similar to those described in chapter 3 for the non-adhesive hydrogels, the principal difference being in the percentage of the components used to form the gels.

PEG 1000DM has been reduced from a major component to a minor one resulting in a decrease in cross-link density. A similar effect was also achieved by reducing the percentage of the cross-linker, methylene-bis-acrylamide. Consequently, the gels were less brittle and could take up more water. Glycerol is now the largest component of the gels at 40% followed by SPI at 30-35%. This gives the gel a high affinity for water which in turn enhances adhesion. Other water soluble interpenetrant polymers were investigated to see if the adhesion and cohesion of the gel could be improved.

4.2 Components for Skin Adhesive Hydrogels

[A] Unsaturated water soluble ionic monomer: SPA, SPE, SPI, SPV and NaAMPS were used, because they are very hydrophilic giving a high affinity for water absorption and they provide a range of functional groups and so should give slightly different properties. Their structures are shown in chapter 2.

[B] Glycerol. Glycerol reduces the effects of evaporation because its polar groups interact with the water strongly.

[C] Water. This is used to alter the pore structure to enhance permeability at lower water contents than might otherwise be acceptable. Sufficient water should be added to enable the chains to move but the amount of water added should be less than the gel's EWC because partial hydration of the gel gives it an affinity for water and enhances adhesion.

[D] PEG 1000DM. This component provides a photopolymerisable network which can be expanded with other hydrophilic components. PEG 1000DM was chosen over

PEG 600DM because it provides fewer cross-links due to the shorter chain length. Too many cross-links would restrict water uptake and gel expansion as well as decreasing flexibility and increasing brittleness. A large volume of PEG 1000DM would have the same effect therefore only a small amount was used.

[E] A water soluble interpenetrant polymer. Initially HPMC has been used to provide a means of controlling the viscosity of the gel. However this will be replaced by other naturally derived interpenetrant polymers frequently used for other skin adhesion applications, they include gum karaya, gum locus bean and gum xanthan (US Pat. No. 1391278)[62].

[F] Cross-Linking Agent. Methylene-bis acrylamide has been used in small amounts, less than 0.5%. Larger amounts would decrease adhesion and increase brittleness.

[G] A Photoinitiator. Irgacure 184 was used as it is currently used in skin contact and ophthalmic hydrogels.

4.3 Determination of the Quantity of Polyethylene glycol 1000DM Required

To produce non-adhesive gels PEG 1000DM was chosen because PEG DMs of lower molecular weight were of inferior strength and created brittle gels. PEG 1000DM's role is to provide a photopolymerisable network which can be augmented with other hydrophilic components. High levels of PEG DM were used in the non-adhesive gels, the levels of PEG DM were greatly reduced to produce adhesive gels. PEG 1000DM was a major component in the non-adhesive gels but in the skin adhesive gels it exists only as a minor component. This is because the cross-link density must be reduced to decrease the brittleness of the gels and to provide more space between cross-links for water to reside. Since, the higher the gel's affinity for water the more adhesive the gel is likely to be.

To produce skin adhesive hydrogels set values of ionic monomer (SPI), glycerol and water was used at 30%, 40% and 30% respectively. This produced satisfactory gels

which could be used to analyse the effects of varying the amounts of other components. PEG 1000DM was the first component to be analysed in this way.

A series of gels were made from a standard formulation where only the percentage of PEG 1000DM was varied and the adhesiveness and quality of the resultant gels were studied. The formulations investigated are shown below.

SPI (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)	HPMC (%)	PEG 1000 DM (%)	M bis A (%added)
34	40	26	0	1	2	0.5	1
34	40	26	0	1	2	1	1
34	40	26	0	1	2	2.5	1
34	40	26	0	1	2	5	1
34	40	26	0	1	2	10	1

Table 4.1 Composition (w/w) of gels used to test the effect of PEG 1000DM on adhesion and gel quality.

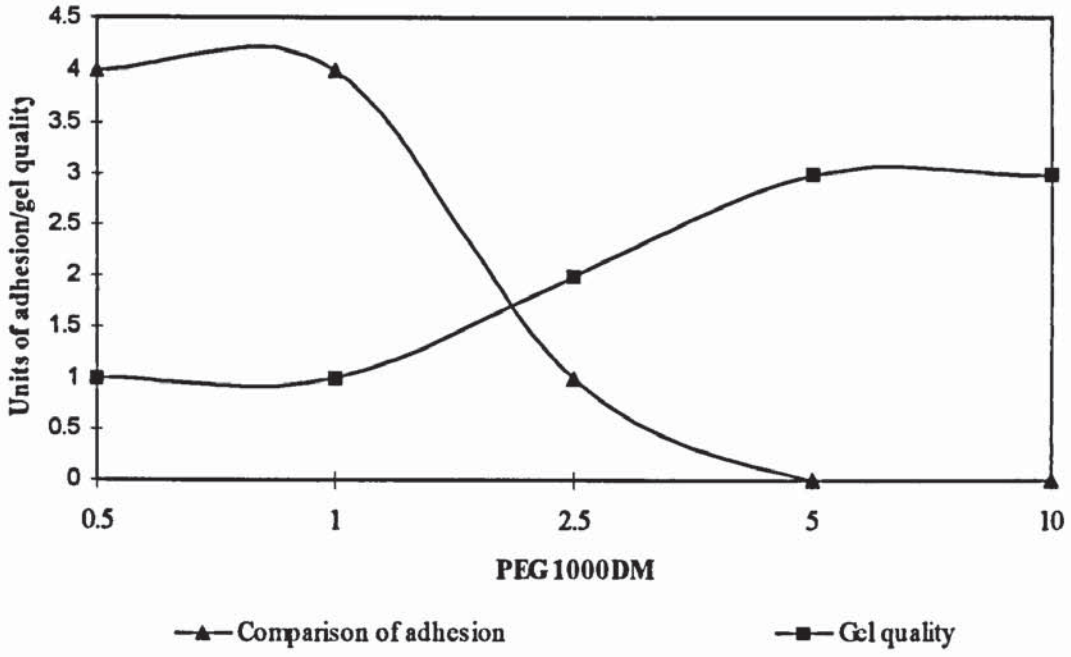


Figure 4.1 The effect of PEG 1000DM on adhesion and gel quality.

The results show that the quality of the gels improved as the percent of PEG 1000DM increased but their tackiness decreased. If the PEG 1000DM exceeded 2.5% the gels were virtually non-adhesive and if the PEG 1000DM was too low, such as 0.5%, the gels were of poor quality. A value of 1% PEG 1000DM was chosen to produce skin adhesive gels with a view to increasing the quality of the gel by the modifying the amount of cross-linker and by alteration of the interpenetrating network by either increasing the percentage of interpenetrant added or by using an alternative, or combination, of interpenetrants.

4.4 Determination of the Optimum Cross-link Density for Skin Adhesive Hydrogels

A chosen formulation known to produce adequate skin adhesive gels was chosen, as before, and used throughout these experiments to enable the cross-link density to be studied. Previous non-adhesive gels had been produced using 1% added cross-linker and this was believed to be too high as the gels produced were some what brittle. Reducing the cross-link density provides more space for water molecules and hence increases the EWC of the gel in addition to reducing the fragility of the gel. With this information, the cross-link density was studied from 0.1 to 1% in steps of 0.1%. The formulations used are shown in the table below.

SPI (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)	HPMC (%)	PEG 1000 DM (%)	M bis A (% added)
34	40	26	0	1	2	1	0.1
34	40	26	0	1	2	1	0.2
34	40	26	0	1	2	1	0.3
34	40	26	0	1	2	1	0.4
34	40	26	0	1	2	1	0.5
34	40	26	0	1	2	1	0.6
34	40	26	0	1	2	1	0.7
34	40	26	0	1	2	1	0.8
34	40	26	0	1	2	1	0.9
34	40	26	0	1	2	1	1

Table 4.2 Compositions (w/w) of gels used to determine the effect of methylene-bis-acrylamide on adhesion and gel quality.

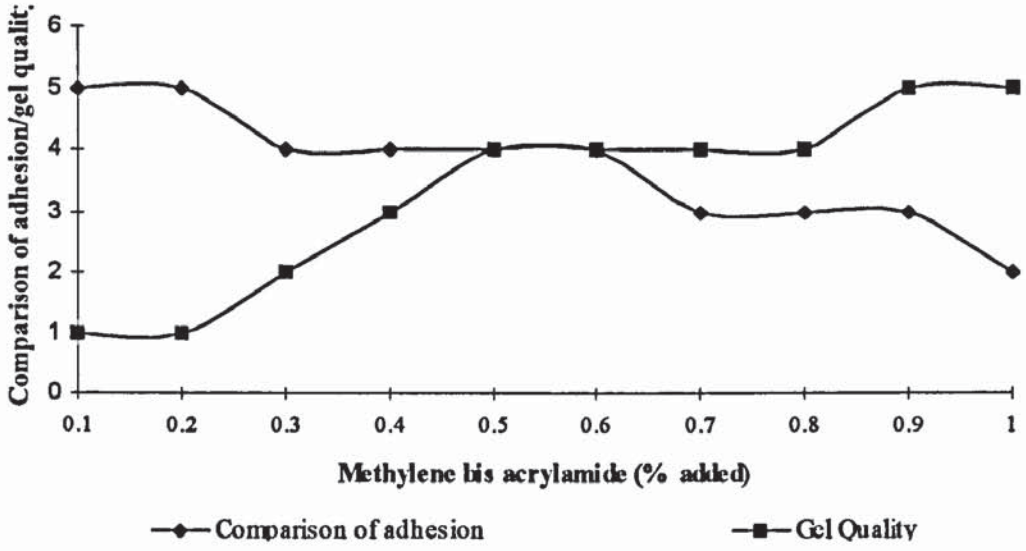


Figure 4.2 The effect of methylene-bis-acrylamide on adhesion and gel quality.

The gels were found to be stickiest when a lower percentage of cross-linker was used, however in this case, the quality of gel was poor forming more of a tacky liquid than a gel. With a higher cross-link density the gels were strong and well formed, unfortunately, this was at the expense of adhesiveness.

Between 0.4 and 0.7% cross-linker the gels were of adequate quality and adhesivity for the purpose of skin adhesion, with 0.5 and 0.6% being the optimum amount of cross-linker for both gel quality and adhesion. This value may appear to be unexpectedly high in comparison to other patented skin adhesive gels, however, if we compare other monomers which may contribute to cross-linking we find this may not be the case. Many formulations use lower molecular weight PEGs, e.g. PEG 400DM, with 0.1-0.2% cross-linker. This gives a cross-link density of similar values to that produced using PEG 1000DM and the optimum values of cross-linker quoted above.

4.5 Determination of the Best Ionic Monomer to Make Skin Adhesive Gels

A range of ionic monomers were tested to determine which produced the best quality skin adhesive gels under the set of conditions specified. It was assumed those with the highest EWC would be the most skin adhesive due to their high relative hydrophilicity

which in the adhesive gels is thought to remove any lubricating water and present an adherent surface. The six ionic monomers tested were SPA, SPE, SPI, SPP, SPV and NaAMPS.

Monomer	Monomer (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure184 (%added)	HPMC (%)	PEG1000 DM (%)	M bis A (%added)
SPA	34	40	26	0	1	2	1	0.6
SPE	34	40	26	0	1	2	1	0.6
SPI	34	40	26	0	1	2	1	0.6
SPP	34	40	26	0	1	2	1	0.6
SPV	34	40	26	0	1	2	1	0.6
NaAMPS	34	40	26	0	1	2	1	0.6

Table 4.3 Compositions (w/w) of gels used to investigate the effect of different ionic monomers on adhesion and gel quality.

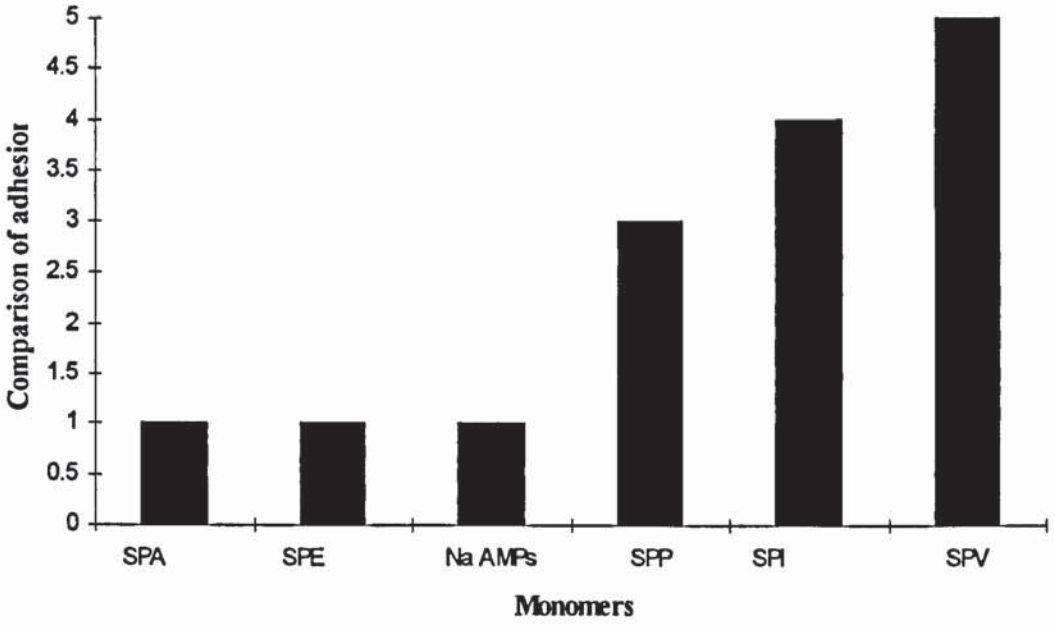


Figure 4.3 The tackiness of ionic monomers SPA, SPE, NaAMPS, SPP, SPI and SPV.

SPA initially formed an adequate gel lacking adhesiveness. The quality of the gel deteriorated rapidly overnight by precipitating out to form a dry, white, rubbery polymer unsuitable for skin adhesives under the present conditions. SPI has two potassium salts,

double the number than that of SPA and a higher EWC. The gels produced by SPI are of good quality and very adhesive. SPE formed a good quality of gel unfortunately the gel was not adhesive enough in a similar manner to that of NaAMPS. SPP with a similar structure to SPE possessing a peptide group in place of a carboxylic group showed slightly better adhesion.

SPV produced exceptional gels which were very tacky and adhesive and the quality of gel was of above average. SPV differs from the other monomers because it possesses a benzene ring with a charged nitrogen and an oppositely charged sulphur group. SPV had an adequate EWC but its skin adhesiveness is likely to be due to its pK_a value of pH6.5 close to the pH of skin (5.5). SPA, SPI and SPE all have an approximate pK_b of pH9 and pK_a of pH3. These findings resulted in SPV being used to try and produce the optimum skin adhesive hydrogel.

It should be noted that these results are unexpected as many current skin adhesives are known to contain NaAMPS or SPA. However, the adhesivness may differ due to the different additional components, the ratio of components and the condition under which the gels are produced such as length of exposure to UV.

4.6 Varying the SPV to Water Ratio to find the Optimum Formulation for Skin Adhesive Hydrogels

SPV displayed good potential as a material for skin adhesive gels. Therefore a range of gels were made using SPV as the ionic monomer while varying the content of water and glycerol.

SPV (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure184 (added %)	HPMC (%)	PEG 1000 DM (%)	M bis A (added %)
30	40	30	0	1	2	1	0.6
31	40	29	0	1	2	1	0.6
32	40	28	0	1	2	1	0.6
33	40	27	0	1	2	1	0.6
34	40	26	0	1	2	1	0.6
35	40	25	0	1	2	1	0.6
36	40	24	0	1	2	1	0.6
37	40	23	0	1	2	1	0.6
38	40	22	0	1	2	1	0.6
39	40	21	0	1	2	1	0.6
40	40	20	0	1	2	1	0.6

Table 4.4 Compositions (w/w) of gels to determine the optimum ratio of water to ionic monomer.

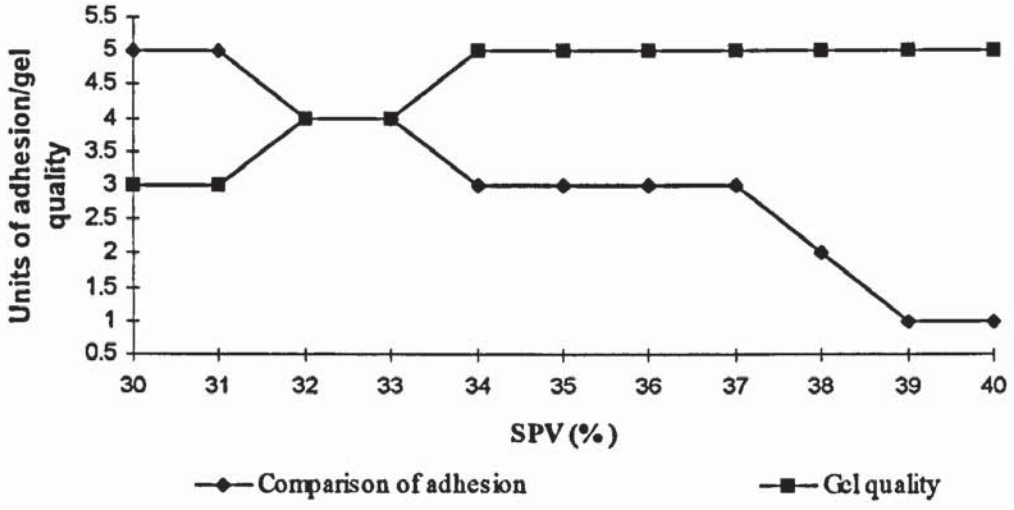


Figure 4.4 The effect of SPV on adhesion and gel quality.

Initially, upon production, the gels all showed excellent adhesive properties in comparison to other ionic monomers. However, this property is short lived. After only a few days, the gels become rigid and almost non-adhesive. It was thought that the adhesion was lost due to dehydration of the gel.

The EWC of non-adhesive gels are lower for SPV than for example SPI. This may result in SPV losing water faster than SPI and becoming non-adhesive. Thereby rendering SPV ineffective as an adhesive because gels will be required to be stored for an indefinite duration prior to use. Figure 4.4 shows the adhesion properties and quality of gels only a few hours after production, preceding dehydration. However, adhesion is virtually lost after a few days.

4.7 Combination Gels

The excellent initial adhesive properties of SPV might last longer if combined with another ionic monomer which does not lose water as rapidly. A few trial samples should be tested ideally within the range of 33-36% ionic monomer, the optimum adhesiveness of SPV under the above conditions.

SPV produced highly adhesive gels which unfortunately lost their tackiness after a few days due to dehydration, much the same as SPA. SPP and SPE both form adequate gels which do not dehydrate rapidly, hence, SPE and SPP were chosen to produce combination gels with SPV in attempt to reduce SPV's dehydration time and increase gel quality.

Initially two gels were produced. The first gel consisted of 36% ionic monomer, with 18% being SPE and 18% being SPV. The second had SPP in place of SPE. Both gels were adhesive and of good quality. The gel containing SPE had no residue on the surface, a desirable trait for skin adhesive gels, and were found to be tougher. Therefore SPE was chosen over SPP for further investigation. Gels were produced ranging from 30 to 40 % ionic monomer increasing in steps of 1% with equal quantities of SPE and SPV.

SPE (%)	SPV (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure184 (added %)	HPMC (%)	PEG1000 DM (%)	M bis A (added %)
15	15	40	30	0	1	2	1	0.6
15.5	15.5	40	29	0	1	2	1	0.6
16	16	40	28	0	1	2	1	0.6
16.5	16.5	40	27	0	1	2	1	0.6
17	17	40	26	0	1	2	1	0.6
17.5	17.5	40	25	0	1	2	1	0.6
18	18	40	24	0	1	2	1	0.6
18.5	18.5	40	23	0	1	2	1	0.6
19	19	40	22	0	1	2	1	0.6
19.5	19.5	40	21	0	1	2	1	0.6
20	20	40	20	0	1	2	1	0.6

Table 4.5 Compositions (w/w) of gels used to test the effect of increasing the ionic monomers to water ratio.

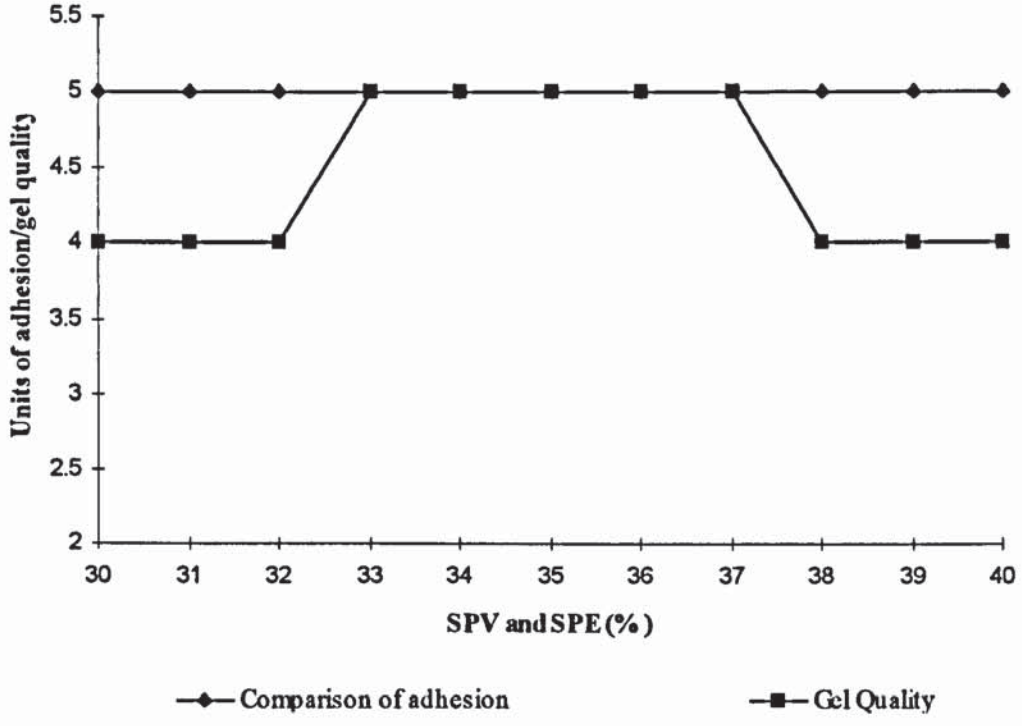


Figure 4.5 The effect of equal quantities of SPE and SPV on gel adhesion and quality.

The gel quality for all of the samples produced was good and no residues were apparent. All the samples produced showed an adequate level of adhesiveness with the most adhesive gels containing 33 to 36 % ionic monomer. The gels at either end of the range were also highly adhesive and showed similar adhesive properties, barely distinguishable

from the optimum range. Perhaps more sensitive methods of testing adhesion will reveal a greater difference in adhesion properties.

If gels consisting of SPV alone and a combination of SPE and SPV are compared, an optimum gel condition, in terms of quality and adhesiveness, can be found in the range of 33 to 36 %. This could be due to the SPV alone or may possibly be the optimum range for most ionic monomers.

4.8 Variation of the SPI to Water Ratio to find the Optimum Formulation for Skin Adhesive Hydrogels

Gels containing the ionic monomer SPI produced good quality gels, which were highly adhesive. Therefore gels containing SPI were investigated further by increasing the ratio of ionic monomer to water.

SPI (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure184 (added %)	HPMC (%)	PEG 1000 DM (%)	M bis A (added %)
30	40	30	0	1	2	1	0.6
31	40	29	0	1	2	1	0.6
32	40	28	0	1	2	1	0.6
33	40	27	0	1	2	1	0.6
34	40	26	0	1	2	1	0.6
35	40	25	0	1	2	1	0.6
36	40	24	0	1	2	1	0.6
37	40	23	0	1	2	1	0.6
38	40	22	0	1	2	1	0.6
39	40	21	0	1	2	1	0.6
40	40	20	0	1	2	1	0.6
41	40	19	0	1	2	1	0.6
42	40	18	0	1	2	1	0.6
43	40	17	0	1	2	1	0.6
44	40	16	0	1	2	1	0.6
45	40	15	0	1	2	1	0.6

Table 4.6 Compositions (w/w) of gels used to determine the effects of increasing the ratio of ionic monomer to water ratio, on gel adhesion and quality.

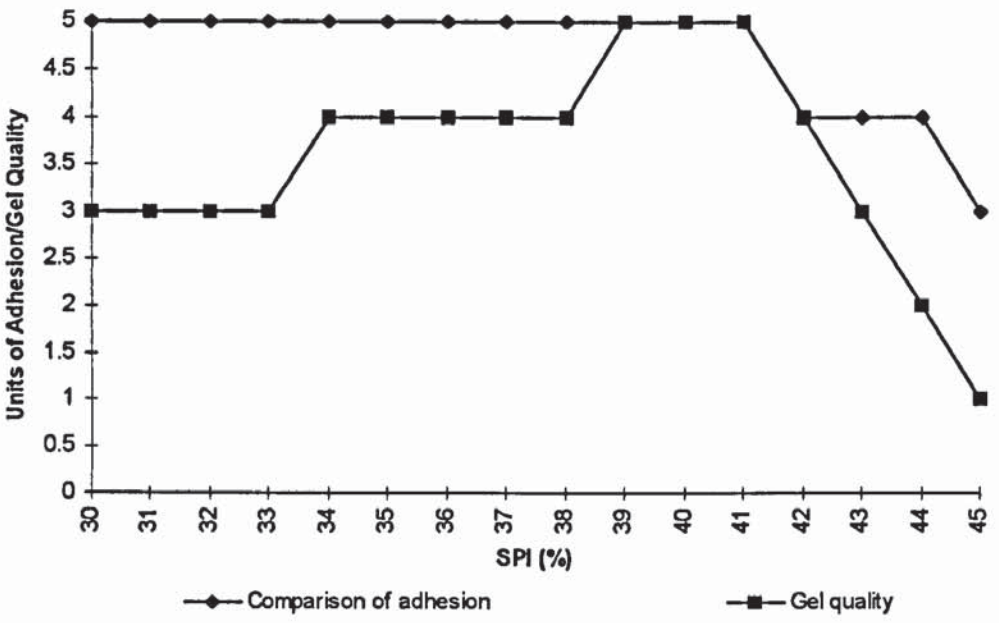


Figure 4.6 The effect of SPI on gel adhesion and quality.

As the ratio of ionic monomer to water increased, the gels adhesiveness increased. However, the gel quality reached a maximum between 39 to 41 % ionic monomer and then decreased. This was due to the decreased solubility of the monomer, the photoinitiator and the cross-linker caused by the decrease or absence of water. Therefore subsequent experimentation with gels containing SPI used an SPI to water ratio of 2:1.

For the set of conditions in which these gels were produced, the gels containing SPI proved to be the best in terms of quality and adhesion, the only drawback being the length of time it required to polymerise gels containing SPI. This could be due to its high molecular weight causing steric hindrance and problems with chain rotation. Although SPI was found to be the best monomer for forming adhesive gels in the formulation and UV lamp system used, other formulations with minor alterations show that for different conditions other ionic monomers are more adhesive than SPI for the conditions used previously. Alteration of the formulation and different polymerisation systems may give different results.

4.9 Water Movement in Gels Produced from SPI and HPMC

In the particular system used the gels containing SPI were found to be the most adhesive. However, when the gels are produced they are not instantly adhesive, in fact, they tend to become more adhesive after approximately 24 hours. This gain in adhesiveness may be linked to water movement after the formulation has polymerised, therefore the water movement within the gels was investigated. 5 gram aliquots of polymer solution with different SPI to water ratios, were poured into containers of equal size and polymerised using UV. The containers accommodating the gels were then weighed and the water movement from the gels recorded by measuring the change in weight after set periods of time. The containers ensured all the gels had the same surface area exposed to the air.

SPI (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)	HPMC (%)	PEG 1000 DM (%)	M bis A (%added)
35	40	25	0	1	2	1	0.6
36	40	24	0	1	2	1	0.6
37	40	23	0	1	2	1	0.6
38	40	22	0	1	2	1	0.6
39	40	21	0	1	2	1	0.6
40	40	20	0	1	2	1	0.6

Table 4.7 Compositions (w/w) of gels used to determine water movement.

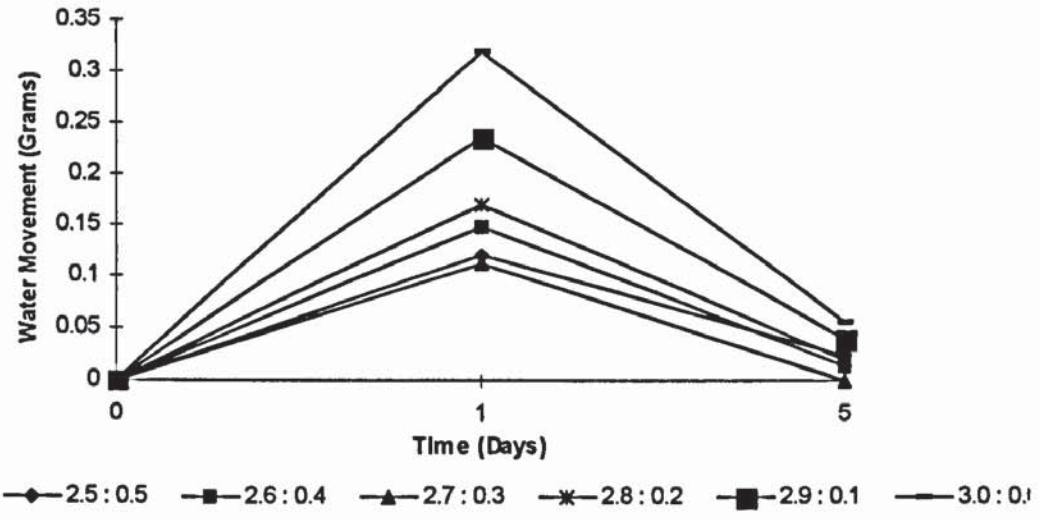


Figure 4.7 Water movement from SPI gels over time.

These results reveal that these low water content gels actually accumulate moisture from the atmosphere. Initially the increase in gel weight is rapid shown by the large increase in the percent of the original gel weight after 1 day. It is at this point that the gels are most adhesive. However, after 5 days the water is lost from the gel as shown by the decrease in the weight measured. Hence a slight decrease in adhesion. Despite the decrease in weight, the weight is higher than that measured on initial production, suggesting the gel contains more water than was initially present.

Another interesting observation is that the greater the monomer to water ratio, the greater the increase in original weight and the increase in water content of the gels follow the same pattern. These gels must have a high capacity to absorb water with the higher capacity gels requiring more moisture to satisfy it, shown by the higher water gain. A point which must be addressed is the long polymerisation time required to produce gels containing SPI. The long exposure to UV and heat may be causing water to evaporate from the gels while they are forming, contributing to their rapid initial requirement for moisture.

4.10 Water Movements in Gels that Contain SPI with Different Polymers

A specific formulation was chosen from the series of SPI containing gels to investigate HPMC, gum xanthan, gum karaya and gum locus bean. This formulation used a 2:1 ratio of SPI to water, details of which are shown in the table below:

SPI (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)	Interpenetrant used (2 %)	PEG 1000 DM (%)	M bis A (%added)
40	40	20	0	1	HPMC	1	0.6
40	40	20	0	1	Xanthan	1	0.6
40	40	20	0	1	Karaya	1	0.6
40	40	20	0	1	Locus bean	1	0.6

Table 4.8 Compositions (w/w) of gels used to determine the effect of interpenetrants used on water movement of the gel.

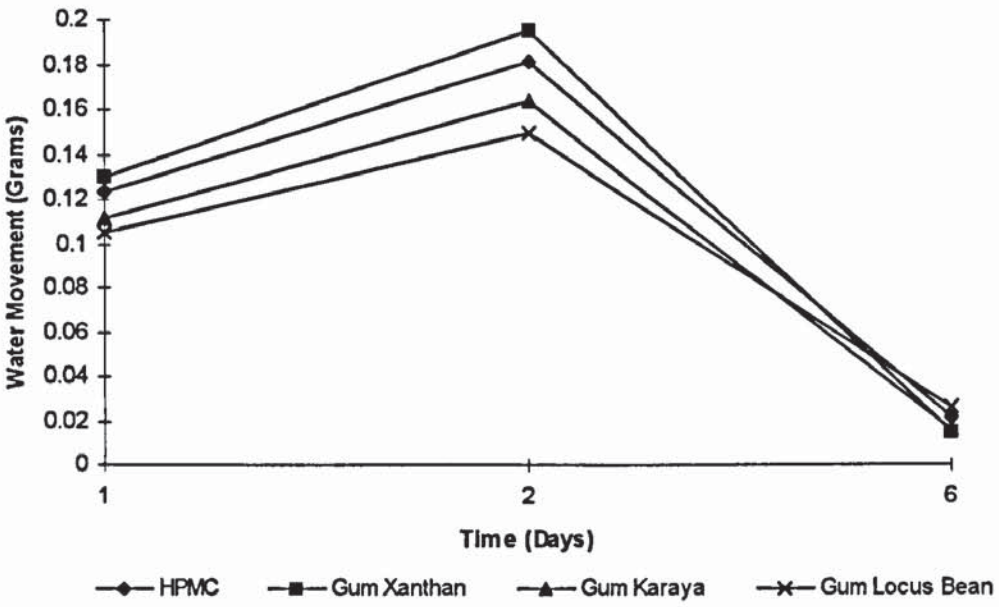


Figure 4.8 Water movement from gels, with different interpenetrants over time.

The results shown in figure 4.8 indicate that the gel are absorbing moisture from the atmosphere. Initially the increase in gel weight is rapid as shown by the large increase in the percent of the original gel weight after 1 day, and again at a slower rate after day two. Six days after formation the water is lost from the gel but is still above the water content it was produced with shown by the small % increase measured in comparison to the large % weight increase shown after day one. Despite the decrease in weight, the weight is higher than that measured on initial production, suggesting the gel contains more water than it contained initially.

All the interpenetrant polymers appeared to follow the same trend in water movement. Unfortunately HPMC was the only interpenetrant which was acceptable to use as the other gums did not form a uniform solution giving non-homogeneous gels.

4.11 The effect of Different Cross-Linkers on the Gel Adhesiveness

Three main components are required for good skin adhesive gels, as before they are:

- An ionic monomer, e.g. SPA, SPE, SPI, SPP, SPV or NaAMPS
- Glycerol
- Water

The main difference between these skin adhesive gels and the former skin adhesive gels is the use of a different cross-linker to dissolve the photoinitiator. The previous series of gels used methylene-bis-acrylamide, a white powder, as a cross-linker and Irgacure 184, which is granular. These were added to the monomer, water and glycerol mixture and put on a shaker to dissolve prior to polymerisation. There was a limited amount of time allowed for the initiator and cross-linker to dissolve as polymerisation could be initiated by sunlight penetrating the glass container. More recent gels used PEG 400DM, Ebacryl II, or IRR 210 as a cross-linker. The liquid cross-linkers dissolve the photoinitiator easily and can dissolve much faster into the monomer mixture.

The ratios of the photoinitiator and cross-linker have also changed to 1% photoinitiator and 0.6% cross-linker (1:0.6), a value arrived at from previous experimental work to 3 parts photoinitiator to 10 parts cross-linker (3:10). This optimum value was determined through extensive work with industrial collaborators, First Water.

The reduction in the over-all amount of cross-linker and photoinitiator mixture added has enabled the gels to become much more adhesive. The exception is SPI which cannot fully polymerise with the low amounts of photoinitiator and cross-linker. SPI which produced the most adhesive gels under the previous set of conditions has been superseded by the gels produced from the new cross-linkers and smaller amounts of photoinitiator. The new gels are far superior in adhesivity probably due to the decreased cross-link density. The components and amounts used are shown below.

Components	**Amount (w/w)**
Monomer	1.95g
Glycerol	1.5g
Water	1.4g
Photoinitiator/Cross-linker	0.0065g

Table 4.9 Compositions (w/w) of gels to determine the effects of different cross-linkers and ionic monomers on adhesion and gel quality.

4.12 Comparison of Cross-linkers

Using the components above six gels were made, each containing a different ionic monomer. All of the cross-linkers used, Ebacryl II, Polyethylene glycol 400 dimethacrylate and IRR 210, gave similar polymerisation results. The solution containing SPI did not polymerise, even when left under the UV lamp for two hours. SPV required an extended polymerisation time whilst the other solutions polymerised rapidly, with SPA and NaAMPS polymerising almost instantaneously. Ebacryl II was the best cross-linker for this application, with IRR 210 being the second most effective agent. This was because the gels produced with the other cross-linkers were much more adhesive and cohesive than gels produced with PEG 400DM. Ebacryl II gave gels with better adhesion properties than IRR 210 but both of these cross-linkers would be effective in producing skin adhesives.

4.13 Conclusion

This chapter looked at the effect the individual components contributed to skin adhesive gels. The components used in chapter three for the non adhesive gels were used but at different percentages in attempt to make the gels adhesive. The first component to be investigated was PEG 1000DM. PEG 1000DM is a hydrophilic polymer which can be augmented with other hydrophilic components as mentioned previously, however it can also serve to increase the cross-link density. The PEG 1000DM was decreased to 1% to enhance potential water uptake but was not reduced further to ensure gel strength was maintained.

Methylene bis acrylamide was reduced from 1% to 0.6% as the previous value was too high and induced brittleness into the gel. It was also decided that other cross-linkers such as Ebacryl II were better cross-linkers as the values required to satisfactorily cross-link gels were much lower, which enabled a more adhesive gel to be produced by means of increased space to accommodate water and increased compliance of the gel.

For the particular set of conditions used, SPI was found to be the best ionic monomer in terms of adhesion. SPV initially appeared to be a good ionic monomer for producing

skin adhesive gels however they became non adhesive as the gels dehydrated and would not be suitable for long term storage. Several interpenetrants were investigated and they were found to be difficult to work with as they did not polymerise homogeneously. HPMC was found to be the best as it was easiest to work with. Although the hydrogels produced were adhesive, they were not as adhesive as current hydrogels on the market and further modification of the formulae was required to improve the gels.

Chapter 5
Adhesion Explored

5.1 Introduction

This chapter explores several theories of adhesion and the difficulties encountered when measuring bioadhesion. This information supports the requirement of a model skin surface to test, as accurately as possible, the adherence of adhesive hydrogels to an adherend. Early measurements were recorded in N/mm to detect subtle changes in peel strength. However, peel strength is subsequently recorded in N/inch as this is the preferred unit utilised to record peel strength. Initially, a negative mould is produced from latex to provide the correct topography of skin in all models to be tested. This mould itself can be used as a skin model too. Three skin models were analysed to determine which is the optimum skin model in terms of reproducibility of the product gel and results of adhesion, economics and most resembled skin in nature.

5.2 Theories of adhesion

The area of bioadhesion is relatively new and no comprehensive theory has yet been established. Many bioadhesion phenomenon exist and no one theory can fully explain each independent bioadhesion phenomenon, therefore the development of bioadhesives has largely been empirical. The theories of adhesion have been classified into four fundamental subsets: mechanical, electrostatic, diffusion and absorption.

5.2.1 Mechanical Theory

The mechanical theory is the oldest explanation for adhesion, in which the adhesive has to flow into the pores and interstices of the material to establish mechanical embedding. The embedded adhesive solidifies and becomes in-extractable. The adhesive force is determined by the work needed to break adhesive extensions off the adhesive mass. Thus, the mechanical theory depends heavily on irregularities of the surface, although specific adhesion is necessary for retention of adhesive within the pore[57].

5.2.2 Electrostatic Theory

This theory states that an electrical double layer is produced at any interface and the consequent Coulombic attraction largely accounts for the adhesion and resistance to separation. This theory was seriously contested by Voyutskii who proposed the alternative diffusion theory[57].

5.2.3 Diffusion theory

The basis of diffusion theory is that adhesion occurs through inter-diffusion of the adhesive and adherend across an interface. This theory has been applied to adhesives involving polymeric materials. Since diffusion of the polymer molecule can be considered as a form of molecular attraction, thermodynamic compatibility between the adhesive and the adherend must exist. In this theory, adhesion is treated as a three dimensional volume process rather than a two dimensional surface process. This is well suited for bioadhesion because a physical entanglement between biomolecules and synthetic polymers frequently occurs[57].

5.2.4 Adsorption Theory

The essence of this theory is that surface forces are involved in adhesion, and that polar molecules or groups if present, are orientated in an orderly way enabling surface molecules of adhesive and adherent to make contact. The possibility of good adhesion can be correlated with wetting, the initial physical process occurring in interfacial bonding. If this theory is correct, the surface energy is expected to correlate with adhesive strength. However, correlation's noted are insufficient to support the theory[57].

5.3 Interactions Involved in Bioadhesion

To understand bioadhesion, it is important firstly to identify the bonding interactions involved in the process. Highly fluid adhesives which are able to penetrate into the cracks and crevices of an adherend can form physical or mechanical bonds. Tissue surfaces present ample opportunities for such bonding, e.g.:

- Primary chemical bond formation

Many bioadhesives can form primary chemical bonds, since a number of functional chemical groups suitable for covalent bonding are present in proteins which are major constituents of biological substrates

- Secondary chemical bond formation

Short-range interactions, such as hydrogen bonding or van der waals attractions, are of sufficient magnitude to contribute significantly to bonding. Adhesive and adherend should be in close proximity for such interactions to be effective. Even relatively simple polymers can demonstrate an extremely high level of adhesion, through very weak but numerous secondary interactions.

5.4 The Effect of Hydration on the Bioadhesive

Some hydrogels become adhesive after hydration. However, there is an optimum water concentration to develop maximum adhesive strength. If the adhesive hydrogel becomes too swollen by water permeation, it will lose its hydrophilic potential and will no longer be able to remove the boundary layer of moisture and become non-adhesive. Degradation of the adhesive bond in water or a humid environment has a tendency to cause a lack of adhesive durability. The effect of the total amount of water available for hydration on the adhesive property of various hydrogels depends on the type of polymer and this makes it difficult to compare adhesive strength under the same conditions.

5.5 The Effect of Hydration on the Biological Adherend

Effective adhesion can only occur when an adhesive and adherend are brought into molecular contact. Such interfacial contact is the first requirement of good adhesion. The presence of water and other fluids on the surface of adherends may prevent full effective possible interactions at the interface. If adhesive bonds cannot displace surface contaminants, adhesion failure can occur due to a weak boundary layer. Poor adhesion may also occur due to the unavailability of binding sites because of the presence of

water. The greatest disruptive effect of water in adhesive bonds is likely to occur with polymer systems that rely primarily on hydrogen bonding for adhesive forces.

Dried hydrogels display extremely aggressive adhesion to moist soft tissues. They may function by dehydrating moist tissue surfaces, swelling, and penetrating surface depressions as in wet adhesion.

5.6 Physical Properties Required of Bioadhesives.

Three physical properties are important for the process of adhesion. They are the flexibility of the adhesive which influence the ability of the adhesive to conform to the adherend, the molecular weight of the adhesive which affects the cohesive strength and the functional groups which ascertain the hydrogen bonding.

5.6.1 Flexibility

The flexibility of an adhesive is important to permit the latter to conform to the adherend. The flexibility of a polymer backbone is influenced by the steric effect of substituent side groups. As the size of the substituent side group becomes larger, chain flexibility is considerably impaired. London dispersion forces, which are significant in forming associative structures, act at a distance of approximately 4 Angstrom and require intimate contact. Thus, it is understandable that adhesiveness is influenced by flexibility of the adhesive molecule. If side chains are flexible they can confer internal plasticisation to the whole polymer structure. When a high degree of internal plasticisation is achieved, the product becomes tacky and is suitable as an adhesive. Increased cross-linking obviously reduces chain flexibility and a decrease in bioadhesive performance is expected[57].

5.6.2 Molecular Weight

Higher molecular weight leads to higher cohesive strength and reduces creep due to the greater degree of chain entanglement which results from longer chains. The adhesive force increases with polymer molecular weight until a plateau value is reached. Beyond a

critical optimal molecular weight, adhesion may be reduced due to a limited penetration of the adherent surface by the adhesive polymer as a result of their constrained mobility. Within any one molecular type, chain length may be the key determinant of adhesive strength. The general observation is that the longer the chain length, the better the bioadhesion. Side-chain length also influences bioadhesive abilities[57].

5.6.3 Functional groups

Effective adhesives usually contain numerous hydrogen bond forming functional groups and hydrogen bonding appears to play a major role in wet adhesion. The excellent performance of adhesives containing aliphatic hydroxyl groups with polar substrates can be explained by the formation of hydrogen bonds. The hydrophilic nature may enhance the cohesive properties of the adhesive by minimising the slippage of the polymer chains[57].

5.7 The Fundamentals of Skin Adhesion

If an adhesive is to adhere to an adherend one fundamental requirement must be satisfied, that is, the measured surface energy of the adhesive must be equal to or less than that of the adherend in order for the adhesive to effectively 'wet' the adherend[16].

5.7.1 Determination of the surface energy of skin

One method of determining skin surface energies involves the measurement of equilibrium contact angles on an adherend, in this instance skin, for a series of liquids of different surface tensions, and extrapolating to zero contact angle to define the critical surface tension of the solid surface under investigation. This technique recorded the surface energy (critical surface tension) of clean, dry human skin to be 28-29 dyn cm-1. This value increases when the skin is dirty or unwashed.

The stratum corneum consists of lipophilic and hydrophilic domains, hair follicles and sweat glands. The hydrophilic domains consists mainly of keratin. Most of the stratum corneum's 20% water content lies in the keratin layers between the horny cells. The

horny cells contain lipids in which the filaments are dispersed. The keratin is tightly cross-linked by about 20% accounting for its relatively rigid and impermeable structure. The keratin layer is thought to be relatively impermeable whereas the lipid domain is more permeable. The elasticity of skin is related to the water content and age. Older people tend to have drier, less elastic skin. Skin which has been made to take up excessive amounts of water, for example, by sweating under an impermeable skin adhesive, tends to be more elastic.

Clean dry skin is mostly lipophilic and therefore has a low surface energy while wet or unclean skin is more hydrophilic, possessing a higher surface energy. Thus, the clean dry is predominantly lipophilic in its characterisation. Polar materials such as hydrogels adhere to the skin are possibly the result of the skin being slightly wet and perhaps due to the presence of hair follicles and sweat glands which contain aqueous channels.

Contact-angle goniometers have been used to calculate surface energies and more specifically the critical surface tension. The measurements show an increase of surface energy with increases in relative humidity and temperature of the skin. The range measured is from 38-56 dyn cm-1. Determining the surface energies of bioadhesives can also be obtained using this method[16].

5.7.2 Kinetic requirements for skin adhesion

During application, the adhesive must be able to flow sufficiently to promote intimate contact between the adhesive and adherend. The earliest attempt to quantify this requirement was made by Dahlquist, and it leads to the following parameters:

Compliance of adhesive > 10^{-6} cm^2 dyn^{-1} or, Modulus of adhesive = 10^6 dyn cm^{-2}.

Adhesive materials that satisfy these criteria have the ability to stick but the parameters do not define its pressure-sensitive nature. Several techniques exist to measure bioadhesion and they include tack (quick stick), peel adhesion and shear strength. All three provide measurements of different aspects of a single adhesive. Tack is a measurement of how easily, in terms of applied pressure, and how quickly a given

adhesive can be applied to a chosen substrate. Peel adhesion, conversely, is a measure of how difficult it is to remove the adhesive following attachment to an adherend. Shear strength is a measure of cohesive strength which gives an indication of the ability of the adhesive to peel cleanly away from the adherend without leaving a residue.

Skin adhesives have unique rheological properties. The adhesive should be easily deformed in a fraction of a second. Dahlquist found the 1 second compliance of a typical pressure-sensitive adhesive having good probe tack to be 10^{-6} cm^2/dyne.

Tack is generally thought of as a surface property, although the values also depend on the material to which the adhesive is laminated, as well as contact time, contact pressure and delamination rate. Hence, tack measures surface as well as viscoelastic properties of the adhesive and adherend. Overall tack can be considered as a short term measurement and gives the initial tendency of the adhesive to adhere to the skin.

Peel adhesion testing again has many variables such as contact pressure and time against the substrate, the angle of peel and the withdrawal speed. While tack indicates ease of application, peel indicates ease of removal. Cohesive failure is easily detected in a peel adhesion test but seldom in tack. Yet again, the peel test is influenced by the nature of the backing, the rate of peel and the viscoelasticity of the adhesive.

It must be borne in mind that the above measurements are not true material properties of the adhesive because they depend to some extent upon both the substrate and the backing material attached to the adhesive[16,18].

5.8 Peel Testing

The lack of a universal method to measure the adhesive strength of a synthetic polymer to a biological surface in an unambiguous manner has hindered quantitative evaluation of various bioadhesives. Even for a given method, a small change in variables such as applied force, the rate of removal of adhesive, the contact area, impurities or a variation in the characteristics of biological adherends, result in completely different values so that

the measured bioadhesiveness tends to be subjective. Additionally, there is more than one type of stress which can be important in assessing adhesive strength.

It should be considered that surface irregularities and minute perturbances prevent perfect contact between adhesive and tissue, which results in an imperfect interface. Thus, the effective area of contact is uncertain and difficult to determine, and the force required to separate the surfaces gives no clue as to the true strength of the bonding at the points where contact does, in fact, occur. Despite these problems, the best experimental test to date to examine bioadhesion is the peel test[77-79].

For both peel tests, the backing of the adhesive is important. Melinex was found to be too rigid and melts under the UV lamp, whilst foam was too weak. The 'backing' side of silicon coated release paper was found to be ideal as it was strong, flexible and held the adhesive well.

The substrate on which the adherend is adhered can be changed to suit the material tested and will be investigated later in this chapter. To compare the 90 and 180 degree peel tests, human skin, rubber and metal substrates were used. Human skin was used as it is the intended site for hydrogel adhesion, rubber was utilised because it is flexible, durable and uniform and metal (steel) was used as that was the chosen substrate for peel tests performed by Cha *et al*[80].

5.8.1 The 90 Degree Peel Test

This perpendicular peel test ensures the adhesive is peeled from the solid support by a grip directly above the end of the adhesive at an angle of 90 degrees. A diagrammatic representation of the 90 degree peel test is shown in chapter 2 figure 2.8.

The peel strengths obtained using a NaAMPS bioadhesive are recorded below. The first set of results represent the first adherence of the bioadhesive to the adherend, the second set of results are derived from the same bioadhesive sample used in the first experiment but pressed down and peeled again while the third is, again, the first experiment but

pressed down and re-peeled after already being measured a second time. This procedure was performed to determine the suitability of the material for removal and repositioning.

5.8.1.1 The Adhesive Capability of an Adhesive on Different Substrates on the 90 Degree Peel Test

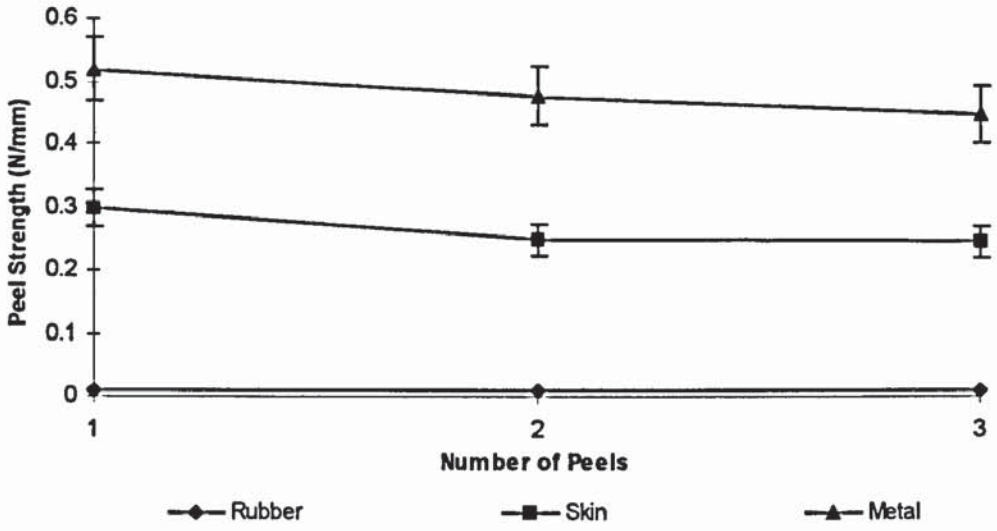


Figure 5.1 The 90 degree peel test using a NaAMPS hydrogel peeled from 3 substrates: rubber, skin and metal.

5.8.1.2 Conclusion

Figure 5.3 shows that the peel strength does not decrease appreciably upon repetitive peeling for the adhesives tested. Initially there is a slight loss but after the second peel, the peel strength remains more or less constant. This is a very desirable property for a skin adhesive which may be required to be removed and repositioned on the body. The peel tests show rubber and metal not to be good skin substitutes however the results obtained were reproducible and can be used for comparison of the adhesives on different substrates.

5.8.2 The 180 Degree Peel Test

This Vertical Peel Test peels the adhesive from the solid surface by a grip directly above the end of the adhesive. A diagrammatic representation of the 180 degree Peel Test is shown in chapter 2 figure 2.7. Only one set of experiments is shown as subsequent runs are unreliable due to the deformation of the gel after its first use.

5.8.2.1 The Adhesive capability of an adhesive on different substrates on the 180 Degree Peel Test

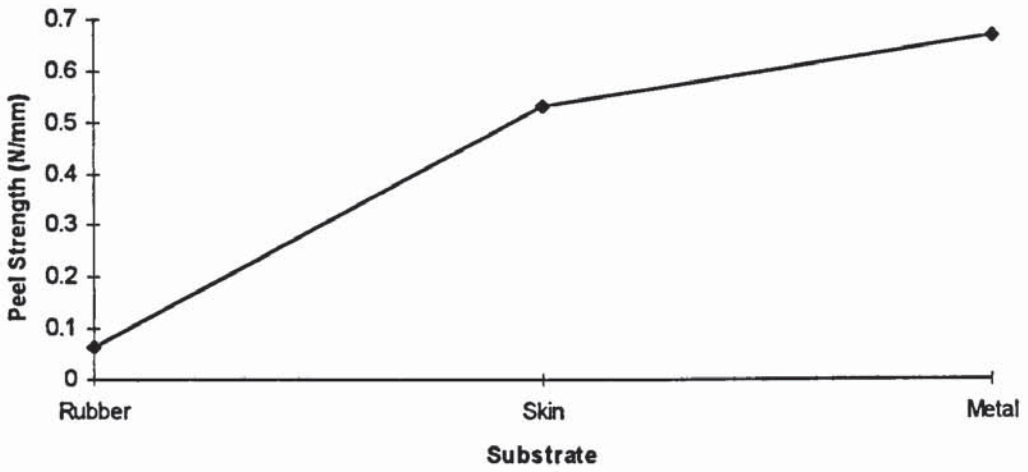


Figure 5.2 The 180 degree peel test using a NaAMPS hydrogel peeled from 3 substrates: rubber, skin and metal.

5.8.2.2 Conclusion

The 180 degree peel test (figure 5.4) with an optimal adherend can provide comparative results between different adhesives. Unfortunately, the upward peeling back motion of these extremely tacky adhesives, does not give a continuous uniform value due to the stop-start effect. This effect is caused by the adhesive force being overcome by the cohesive force at a given point followed by the return of adhesive force after the point at which the cohesive force has been peeled from the adherend. This results in the recording of peaks and troughs, the peaks where the adhesion is at a maximum and a

trough where the cohesive force has overcome the adhesive force. The angle at which the adhesive is peeled from the adherend seems to enhance the stop-start effect. Therefore the majority of the peel testing was performed at 90 degrees. It was also noted that if the gel was not of uniform thickness then those areas of greater thickness were marginally more adhesive.

5.9 Model Human Skin

Skin is a complex, organised structure composed essentially of protein, lipid and water. The stratum corneum (the outermost layer) is nonviable and has an average water content of 25% of its dry weight. However, under conditions of hydration, this percentage may increase to greater than 75%. This configuration is further complicated by the elevations and depressions resulting in regions of coherent and non-coherent topography.

Experiments performed on human skin panels are often used to obtain data. Unfortunately these tests procedures are costly and difficult, and in addition are variably being influenced by numerous factors including surface morphology and moisture. Moreover, protocol for human testing requires pre-screening for pregnancy and medical conditions, especially those which may be affected by transdermal diffusion of trace amounts of unreacted monomer present in the adhesive formulations.

Since human models present many obstacles, in vitro models using excised human skin and animal models have been studied. These models are unpopular due to their time consuming preparation and highly variable results. One solution is to produce a reproducible synthetic skin model.

A model skin surface is an ideal solution as it eliminates the requirements for costly and variable human skin substrates and because the skin model consists of simple, readily obtainable components, it can be easily and accurately reproduced. The fact that the skin model is synthetic and can be produced from water-swellable but comprise water insoluble proteinaceous material, triglycerides and water, enables the water content to be

varied to study skin of different moisture contents. This permits adhesion to be tested under diverse conditions as in US Patent No. 4877454[81].

5.10 Preparation of the Adherends and their Expected Properties

To prepare the adherends, a negative mould is produced from latex to provide the correct topography of skin in all models to be tested. The mould itself is also a skin model. The latex, triglyceride and economical artificial skin models were analysed to determine which was the optimum skin model in terms of reproducibility of the product gel, results of adhesion, the economics of the mould manufacture and which model most resembled most skin resembling in nature. The method of manufacture of each skin model described below is followed by an explanation of the performance of each mould.

5.10.1 Preparation of a Rubber Skin Mould (Model 1)

The usual process of creating a rubber mould for modelling according to Dow Corning, requires mixing 100 parts SILASTIC 3481 Base to 5 parts SILASTIC 81, a curing agent. However, to create a rubber mould of the arm 100 parts of SILASTIC base was mixed with 10 parts SILASTIC 81-VF. This curing agent requires only 8-10 minutes to cure and form a product which cures more than ten times faster than the original curing agent. The curing rate is furthermore increased by doubling the amount of curing agent employed. This is performed to reduce the time the rubber solution is in direct contact with the skin, in order to minimise the likelihood of skin irritation and also to reduce the otherwise lengthy waiting period required for cure to take place.

The catalysed mixture is spread thinly on the arm and curing is allowed to begin. Before fully set, an additional layer of catalysed mixture is added to achieve a coating of more than 2 mm and this cures at room temperature until tacky. Finally another solution of the same catalysed mixture is prepared. In the latter case 3% by weight of SILASTIC Thixo Additive is added to achieve a paste consistency which can be spread on to the arm to a thickness of approximately 1 cm. This can be removed from the arm and allowed to cure fully for 24 hours. To make a mould covering 6 by 12 cm, the following quantities of material are utilised:

- **First catalysed mixture**

1. 15g of SILASTIC 3481 Base
2. 1.5g of SILASTIC 81-VF

- **Second catalysed mixture**

1. 30g of SILASTIC 3481 Base
2. 3g of SILASTIC 81-VF
3. 1g SILASTIC Thixo Additive

The resulting rubber mould is placed in a tray and used as a negative mould to make a skin model with one surface possessing an imprint of the human skin's topography. Accidental and unwanted transfer of small amounts of silicon material to the model skin was ruled out by comparison of the contact angles of water and diiodomethane when model skin surfaces were made adjacent to silicon and a surface such as Mylar, as performed in the U.S. Patent 4,877,454[81].

5.10.1 The Suitability of Rubber as a Skin Model

This skin model with human skin topography is ideal for testing the adhesion of gels as it provides an alternative to costly and highly variable human skin substrates and consists of a water content similar to human skin which can be varied to simulate differing human skin moisture contents.

Primarily this rubber model is used as a negative mould to produce a model with matching topography to that of the skin. However, this cast could moreover be used as a skin model itself. The material is elastic and rubbery in nature, similar to skin. Additionally this material will not dehydrate and can be repeatedly used without deterioration. A rubber skin model is likely to be good for providing reproducible, comparative results of the adhesive properties of different gels.

5.10.2 Construction of an Artificial Skin Using Triglycerides (Model 2)

[A] A water soluble proteinaceous material is cross-linked to make a water-insoluble but water-swellable material. Materials that satisfy this criteria include porcine or calf skin gelatin, water-soluble collagen, water-soluble bovine globulins, polylysine polyaminoacid copolymers and terpolymers. Gelatin was used as in was inexpensive and readily available.

[B] Di or triglyceridic esters formed from fatty acids of 12 carbons or more. Examples of suitable glyceridic esters may be di or tri glycerides of lauric, myristic, palmitic, stearic and oleic acids. The triglycerides are preferred. The triglyceride used in these experiments was trimyristin (ca 14:0) The ratio of proteinaceous material to glyceridic ester should be between 3.3:1 and 3.5:1. The ratio chosen was 3.4:1.

[C] Water. The water content can be varied to obtain the moisture content of the skin conditions being mimicked. The state of hydration of the human stratum corneum depends on the local relative humidity. The outermost and bottom layer reside in quite different environments resulting in a gradient in water concentration estimated to be 17 and 41 % respectively.

[D] An antibacterial to prevent bacterial contamination. Propylparaben was used.

[E] Sodium hydroxide. This is required to prevent phase separation.

[F] A cross-linker. Formaldehyde satisfied this purpose.

Components	Quantity
Gelatin	10g
Water	85g
Triglyceride	3.4g
Antibacterial	0.05g
Sodium hydroxide (1M)	4.5 ml
Formaldehyde	3.95g

Table 5.1 A skin model constructed from triglyceride.

5.10.2 1 The Suitability of an Artificial Skin Model Comprised of Triglycerides

The components used in this model produced a skin like gel in texture and can be adjusted to contain any desirable water content. The skin-like gel would have to be made prior to testing as dehydration occurs over the course of days. This causes problems of expense. The triglycerides are also expensive and would be too costly to use each time a skin model was required.

A further problem is the use of formaldehyde, which cured the system instantly and so it was hard to add to the system evenly, resulting in irregular curing throughout the gel. Again with expense in mind, it is too costly to conduct repeated experiments with the formaldehyde where an unusable gel would result in wastage of expensive triglycerides.

5.10.3 Construction of an Economical Artificial Skin Model (Model 3)

[A] A water soluble proteinaceous material cross-linked to make a water-insoluble but water-swellable material. Materials that satisfy this criteria include porcine or calf skin gelatin, water-soluble collagen, water-soluble bovine globulins, polylysine polyaminoacid copolymers and terpolymers. Gelatin was used as in was inexpensive and readily available.

[B] Glycerol. Although glycerol ($C_3H_8O_3$) is hydrophilic and triglycerides are hydrophobic, it was chosen to replace the triglycerides because three fatty acid molecules combine with one molecule of glycerol to form a triglyceride. The glycerol alone will contain polar groups similar to many triglycerides and should be adequate as a replacement for the purpose required. As well as being inexpensive and readily available, glycerol is desirably viscous and is known to be used to produce good quality gels for various applications including contact lenses.

[C] Water. The water content can be varied to obtain the moisture content of the skin conditions desired. The state of hydration of the human stratum corneum depends on the local relative humidity. The outermost and bottom layer reside in quite

different environments resulting in a gradient in water concentration estimated to be 17 and 41 % respectively.

[D] An antibacterial to prevent bacterial contamination, such as propylparaben.

[E] Sodium hydroxide. This is required to prevent phase separation.

[F] A cross-linker. Methylene bis acrylamide was used as it is readily obtainable and does not cure instantly.

Components	Quantity
Gelatin	10g
Water	85g
Glycerol	3.4g
Antibacterial	0.05g
Sodium hydroxide (1M)	4.5 ml
Methylene bis Acrylamide	1.0g

Table 5.2 A skin model constructed from economic components.

5.10.3 1 The Suitability of an Economical Skin Model

The most important difference in this skin model is the exchange of glycerol for triglycerides. This greatly reduces the cost and enables more experimentation with the system to be performed.

The consequence of substituting methylene bis acrylamide for formaldehyde is an evenly cured gel. This gel can then have a thin layer of formaldehyde spread evenly on its surface to enhance curing but avoiding over rapid curing since by that stage the methylene bis acrylamide has completed the majority of the fixing. This adapted skin-like gel's major advantage over the initial gel is the fact it is more economical and therefore suitable frequent production, whenever required.

5.10.4 Evaluation of the Adherends

The 90 degree peel test was performed with rubber, two skin substitutes, metal and skin as adherends. It was thought that a rubber mould with human skin topography would be a good substitute for skin to test the adhesion of gels because the material is elastic and rubbery in nature, similar to skin. Additionally, this material would not dehydrate and could be reused repeatedly without deterioration. When tested, the rubber skin model proved to be good for providing reproducible, comparative results of the adhesive properties of different gels but did not show the peel strength to be of the same magnitude as on viable human skin. In fact, if we compare the peel strength of NaAMPS on the rubber mould with that on skin, it can be shown that the peel strength is approximately 25 times less. The peel strength of NaAMPS on rubber being 0.0114 N per mm compared to 0.298 N per mm for viable human skin.

The two skin substitutes failed to be utilised effectively to test the peel strength of NaAMPS as an adhesive. This was due to the inability of the adhesive to adhere to skin substitutes. For an adhesive to adhere to an adherend a fundamental thermodynamic requirement must be satisfied, that is the surface energy of the adhesive must be equal to or less than that of the adherend since the adhesive adheres to neither of the skin substitutes . Both skin substitutes must have a surface energy lower than that of the adhesive and therefore be preventing adequate adhesion from occurring.

The metal plate and skin on the arm of a volunteer proved to be the best for testing peel strength. Both the metal plate and the viable skin enabled reproducible results to be obtained. If the peel strength of NaAMPS on the metal plate is compared with that of skin, it can be shown that the peel strength is higher. The peel strength of NaAMPS on metal is 0.5129 N per mm compared to 0.298 N per mm for real skin, almost double the value. Therefore skin is the most suitable substrate on which to test skin adhesion as no other substrate has properties which closely resemble those of the skin. It should be noted that the peel strength on skin will vary from subject to subject depending upon the lipid and moisture content of their skin and factors such as perspiration and grease. Consequently, gels may adhere to some skin types but not on others.

5. 11 The effect of Thickness on Peel Strength

NaAMPS gels of differing depth were investigated to determine the effect of gel thickness on peel strength. The gels were cut in to strips of 1 inch by 5 inches and the thickness was measured using a micrometer and recorded. These gels were subsequently placed on the forearm of the subject and stuck down as before prior to the 90 degree peel test.

5.12.1 Thickness against Peel Strength

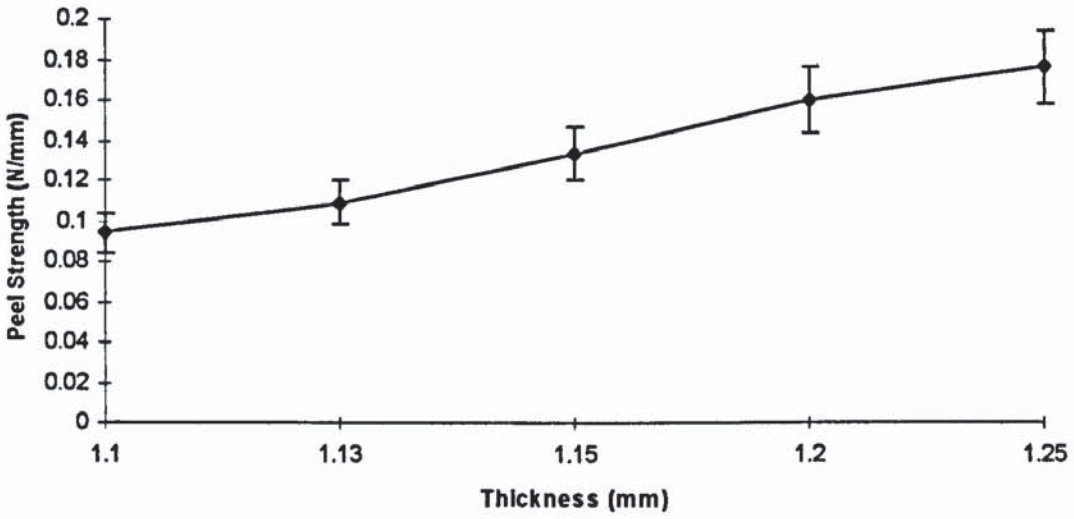


Figure 5.3 The effect of gel thickness on peel strength using basic NaAMPS gels.

As the thickness of the gel increases so does the peel strength, up to a certain limit. Therefore it is important to keep the thickness of the gels constant when comparing different gel compositions. If the adhesive is very thick and strong then the upper layer of the skin can be stripped away revealing the viable skin cells. When subsequent peeling is performed on these viable cells, the peel strength increases because the cells become harder to remove and result in bruising of the skin together with unreliable results. This can be overcome by reducing the thickness of the gels. This effect is also produced by repeated peeling on the same site over a short period of time.

An increased peel force is also experienced with a thicker backing, as there is a larger area under stress, and increased peel rate.

5.12 The Effect of Peel Testing on Skin Injury

Bioadhesive hydrogels function by adhering securely to the skin. However, if the adhesive adheres too strongly, pain is felt on removal. Less adhesive gels can also cause skin trauma if used repeatedly on the same area of skin. Therefore the pain experienced by peeling was investigated to observe the relationship between the peel strength of a pressure sensitive adhesive and skin trauma.

It is important to determine the consequence of peeling pressure sensitive adhesives from skin because they are currently widely used as biosensors, drug delivery devices and wound dressings and they have the potential to be exploited for many more diverse applications. One potential use presently being investigated is the use of adhesive hydrogel as a sealant to prevent leakage from nappies, by adhering the nappy to the body. All such applications require the hydrogel to be in contact with the skin for extended periods of time. In the case of nappies, the hydrogel may be adhered to the skin for 8 hours during sleep and then fresh hydrogel may be repeatedly peeled from the skin as changing occurs throughout the day. Therefore it was important to ascertain the effect the adhesive hydrogels exert on the skin. The surface of several pressure sensitive adhesives were examined by scanning electron microscopy to investigate the surface of the pressure-sensitive adhesives in order to provide information on the condition of removed skin cells after contact with hydrogels over specific periods of time. Yamamoto *et .al* evaluate the materials' affinity for cells quantitatively by direct measurement of the shear force necessary to detach a cell from a the material being investigated. Although this method is interesting, it would be difficult to practice on hydrogels as they would swell aggressively in the medium where measurement occurs[82].

5.13 Preparation of Pressure-Sensitive Adhesives for Scanning Electron Microscopy

Strips of various pressure-sensitive medical adhesive tapes were applied to the inner forearm of the subject under investigation and were peeled off after a specified period of time. For chosen adhesive tapes, subsequent peels of fresh tape were performed at the same site as previous peels. After each peel, small samples of the adhesive were examined under a Cambridge Stereoscan scanning electron microscope. For adhesive hydrogels the water in the hydrogel sample was removed prior to scanning electron microscopy by critical point drying using freon liquid. Thermal images of the adhesive surface were recorded in the form of photographs.

5.14 Comparison of Pressure-Sensitive Adhesives

Seven pressure-sensitive adhesives were examined, six them being commercially used medical adhesives. The peel strength of each adhesive was recorded and the surface of the adhesive examined to provide information on the condition of the skin after peeling. A control thermal image for each adhesive was taken to show the surface prior to adhesion.

Information on the pressure sensitive adhesives are shown below in table 5.3.

Material	Supplier/ Trade Name	Peel Strength (N/Inch)	Removal Period	Test Number	Figures
Steri-strip	3M	-	Control	-	5.4
Steri-strip	3M	-	Instant	1	5.5
Padded Strapping	Boots	0.42	Control	-	5.6
Padded Strapping	Boots	0.42	Instant	1	5.7
Micropore Surgical Tape	Boots	0.55	Control	-	5.8
Micropore Surgical Tape	Boots	0.55	Instant	1	5.9
Waterproof Strapping	Elastoplast	1.58	Control	-	5.10
Waterproof Strapping	Elastoplast	1.58	Instant	1	5.11
Zinc Oxide Tape	Boots	2.18	Control	-	5.12
Zinc Oxide Tape	Boots	2.18	Instant	1	5.13
Fabric Strapping	Elastoplast	3.76	Control	1	5.14
Fabric Strapping	Elastoplast	3.76	Instant	1	5.15
NaAMPS Hydrogel	-	7.42	Control	-	5.16
NaAMPS Hydrogel	-	7.42	Instant	1	5.17
Zinc Oxide Tape	Boots	2.18	2 Hours	1	5.18
Zinc Oxide Tape	Boots	2.18	2 Hours	3	5.19
NaAMPS Hydrogel	-	7.42	2 Hours	1	5.20
NaAMPS Hydrogel	-	7.42	2 Hours	2	5.21
NaAMPS Hydrogel	-	7.42	2 Hours	3	5.22

Table 5.3 Details on the materials used for peel testing. The figures correspond to the ensuing photos, the test number indicates the number of times the material has been adhered to that particular site, removal period is the time period the material is in contact with the skin for, and the control is a S.E.M of the material before being adhered to the body.

5.15 Thermal Images of Adhesive Surface

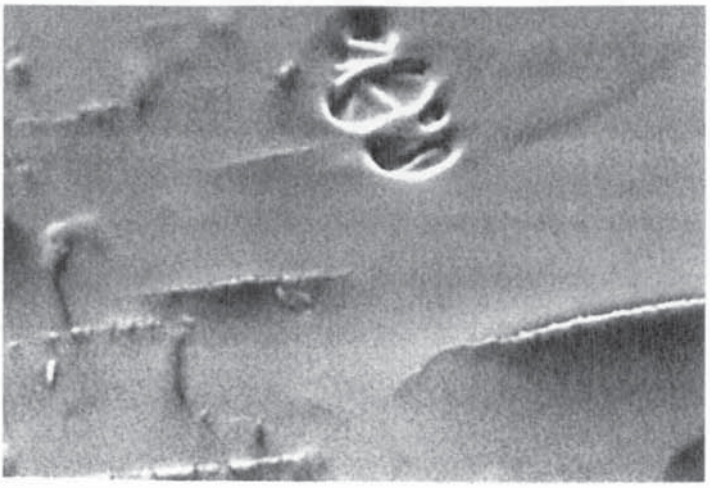


Figure 5.4 S.E.M. Image of a Steri-Strip control on116 x 200 μm magnification at 25kV.

Figure 5.5 S.E.M. image of a Steri-Strip peeled from subjects arm on116x200 μm magnification at 25k.V. Arrows show dead skin cells.

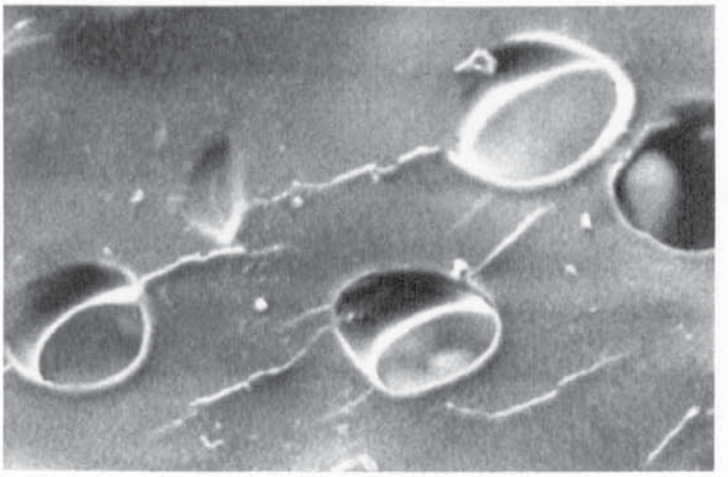


Figure 5.6 S.E.M. image of a Padded Strapping control on 116 x 200 μm magnification at 25kV.

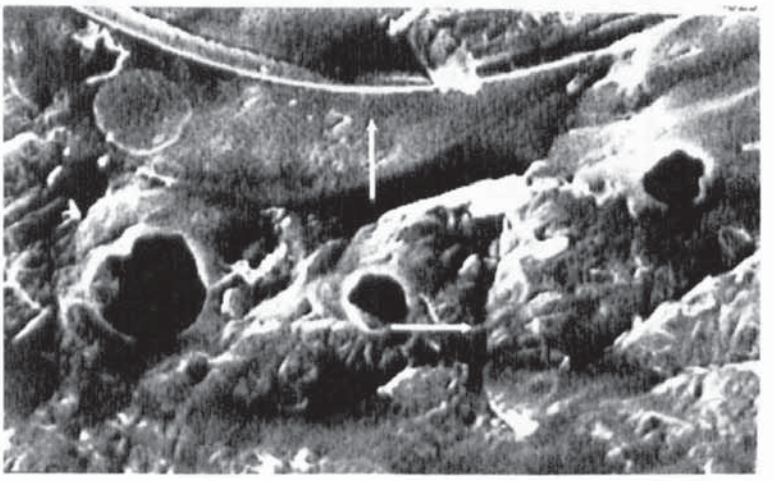


Figure 5.7 S.E.M. image of Padded Strapping Peeled from subjects arm on116 x 200 μm magnification at 25kV. Arrows show dead skin cells.

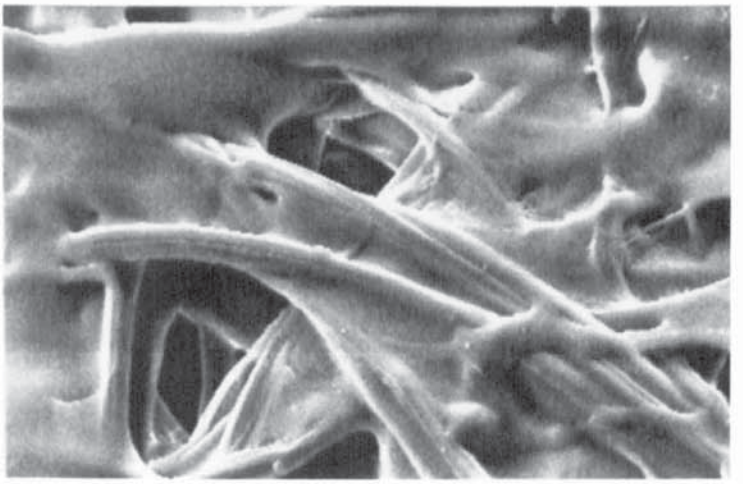


Figure 5.8 S.E.M .image of a Micropore control on 116 x 200 μm magnification at 25kV.

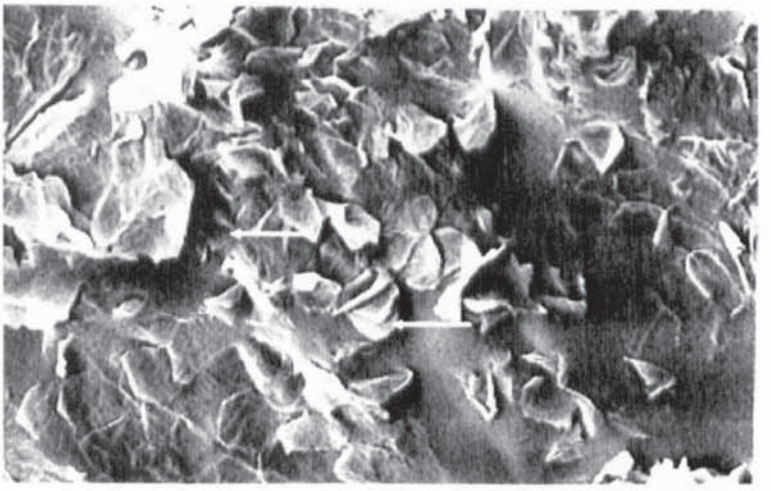


Figure 5.9 S.E.M. image of Micropore peeled from subjects arm on116 x 200 μm magnification at 25kV. Arrows show dead skin cells.

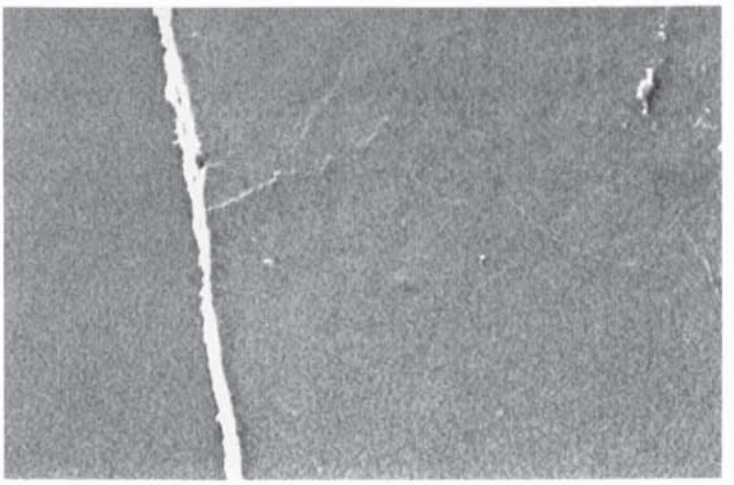


Figure 5.10 S.E.M .image of a Waterproof Strapping control on 116 x 200 μm magnification at 25kV.

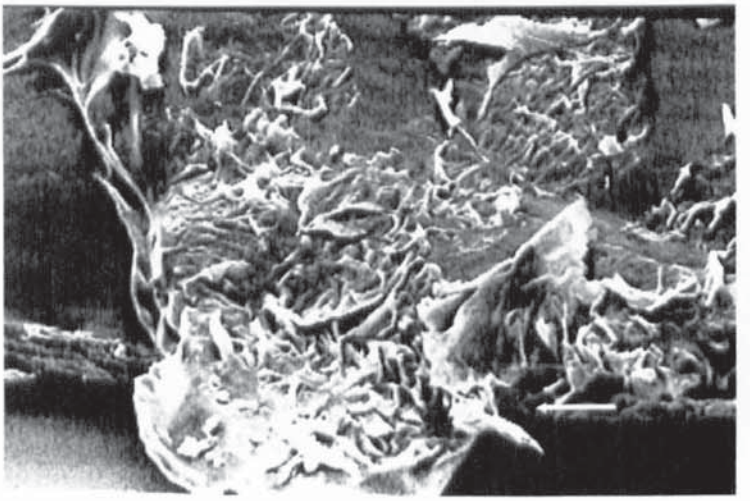


Figure 5.11 S.E.M. image of Waterproof Strapping peeled from subjects arm on116 x 200 μm magnification at 25kV. Arrow show sheet of dead skin cells.

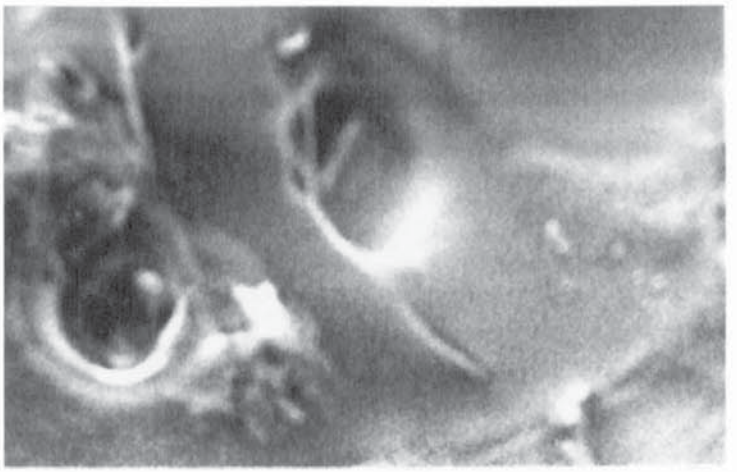


Figure 5.12 S.E.M. image of a Zinc Oxide Strip control on 116 x 200 μm magnification at 25kV Zinc Oxide control.

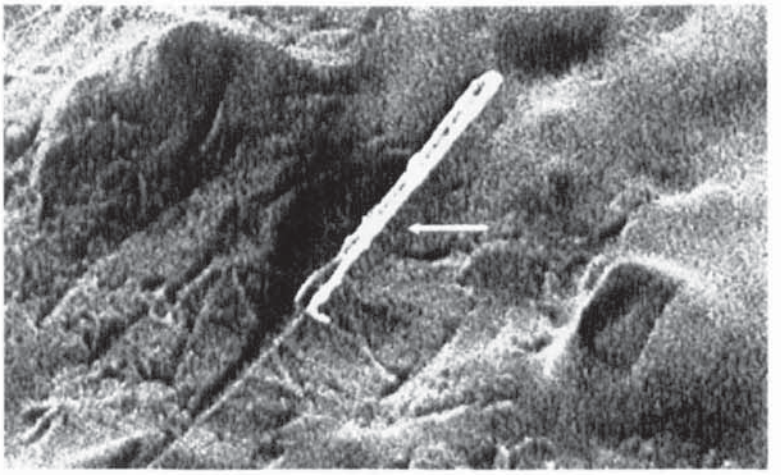


Figure 5.13 S.E.M. image of a Zinc Oxide Strip peeled from subjects arm on 116 x 200 μm magnification at 25kV. Arrows show dead hair and follicle.

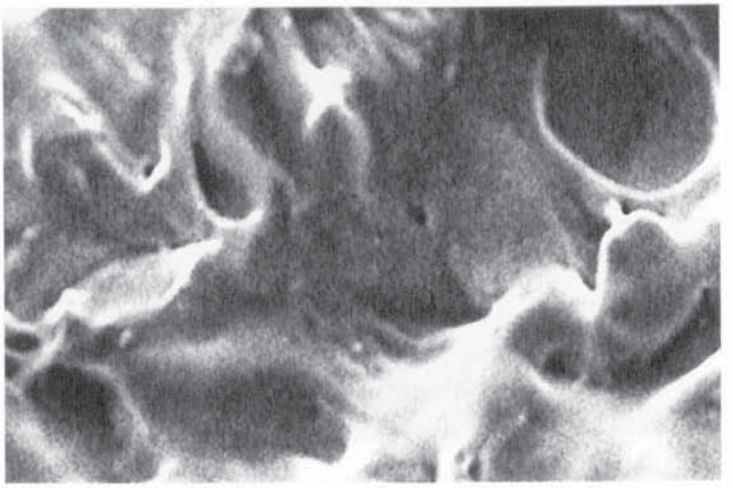


Figure 5.14 S.E.M. image of a Fabric Strapping control on 116 x 200 μm magnification at 25kV.

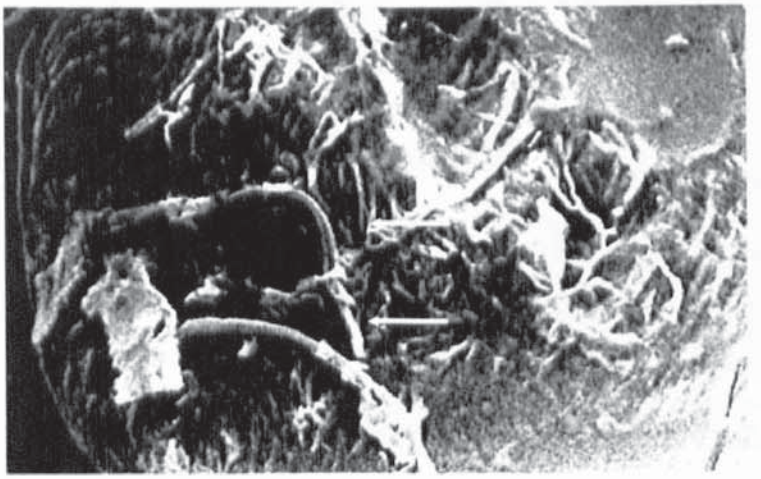


Figure 5.15 S.E.M. image of Fabric Strapping peeled from subjects arm on116 x 200 μm magnification at 25kV. Arrows show dead skin cells and hair.

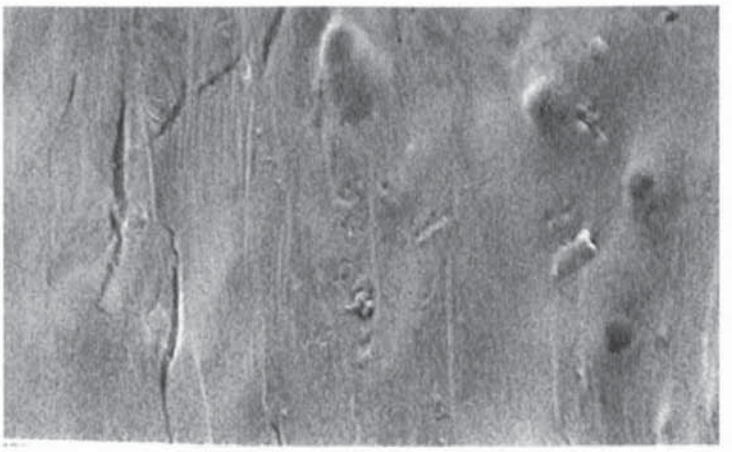


Figure 5.16 S.E.M. image of a Hydrogel control on116 x 200 μm magnification at 25kV.

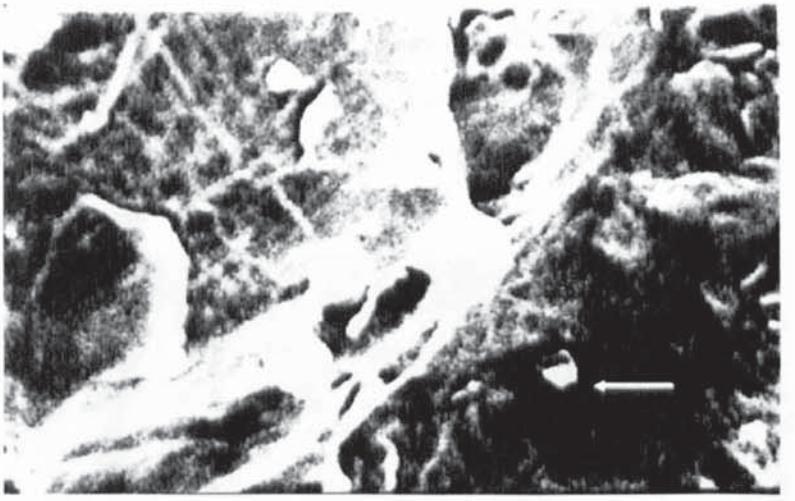


Figure 5.17 S.E.M. image of Hydrogel peeled from subjects arm on116 x 200 μm magnification at 25kV. Arrows show viable skin cells.

5.16 Discussion

Images of the interface of the pressure-sensitive adhesives were arranged in ascending order of peel strength. At the lower peel strengths and instant removal, (Steri-strip, Padded Strapping, Micropore and Waterproof Strapping) the main component on the surface of the adhesive is dead skin cells, with sheets of dead skin cells being pulled off as the peel strength increases. As the peel strength rises above 2N per inch, hairs are beginning to be pulled out of the skin, for example the Zinc Oxide Strip and Fabric Strapping. The hydrogel with a peel strength of 7N per inch initiates the removal of live cells. Therefore it is concluded that as peel strength increases, more debris is removed when an instant peel is performed, with hair and live cells being removed at higher peel strengths. Images of adhesive prior to adhesion on skin were taken to show that the thermograms displayed cell debris not just the adhesive surface.

5.17 Repetitive Peels from the Same Location after a Two Hour Adhesion Period

Hydrogel and Zinc Oxide adhesives were chosen to investigate the effect of peeling the adhesive several times from the same area, each time using a fresh piece of adhesive. The adhesive was removed from the skin almost immediately after adherence had occurred.

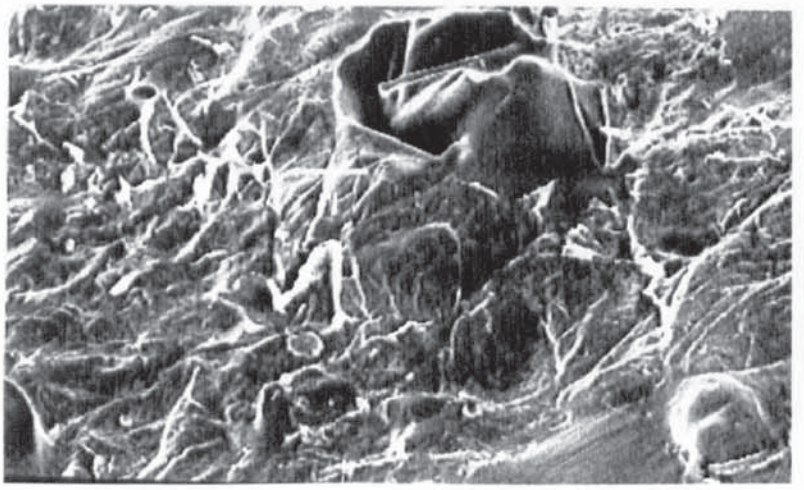


Figure 5.18 S.E.M. image of a Zinc Oxide Strip after first peel from a specific site on the subject's arm on 116 x 200 μm magnification at 25kV. Arrows show dead skin cells.

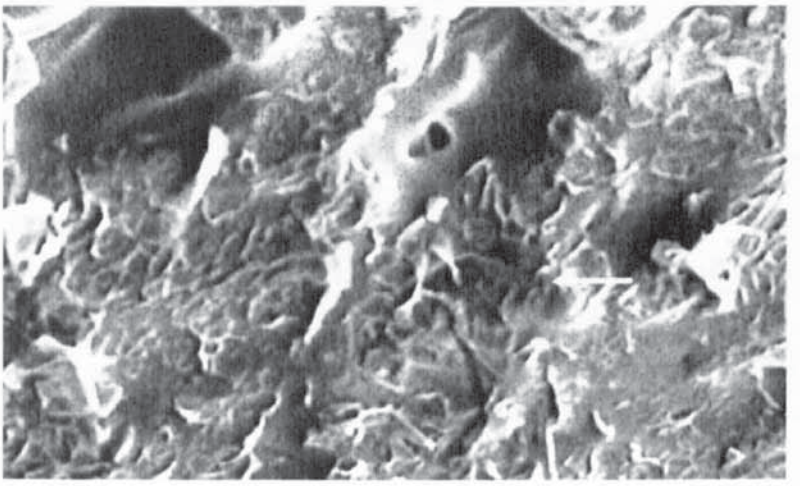


Figure 5.19 S.E.M. image of a Zinc Oxide Strip after the third peel from a specific site on the subjects arm on 116 x 200 μm magnification at 25kV. Arrows show dead skin cells.

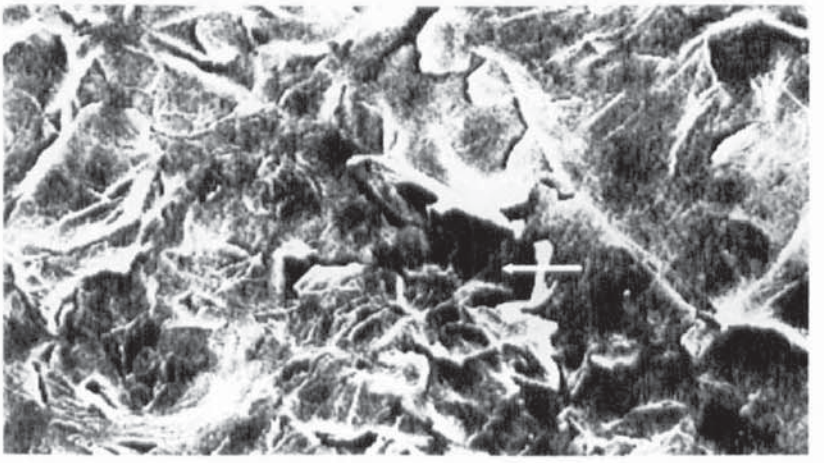


Figure 5.20 S.E.M. image of a Hydrogel Strip after first peel from a specific site on the subject's arm on 116 x 200 μm magnification at 25kV. Arrows show dead skin cells.

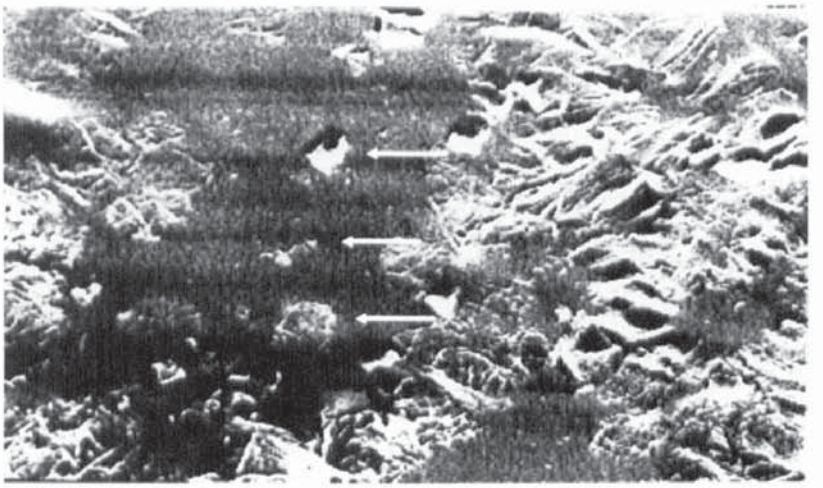


Figure 5.21 S.E.M. image of a Hydrogel Strip after a second peel from a specific site on the subject's arm on 116 x 200 μm magnification at 25kV. Arrows show viable skin cells.

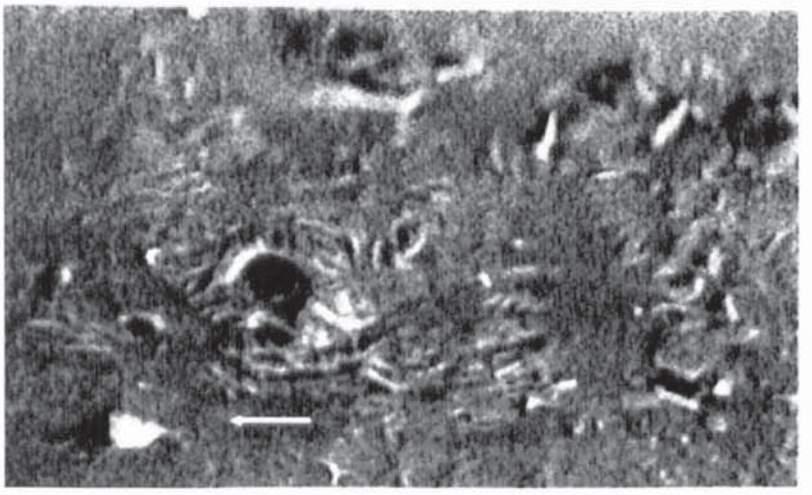


Figure 5.22 S.E.M. image of a Hydrogel Strip after the third peel from a specific site on the subject's arm on 116 x 200 μm magnification at 25kV. Arrows show viable skin cell.

5.18 Results

The Zinc Oxide adhesive showed little change in cell debris collected after each peel over a short period of time. The adhesive appears to only peel off dead surface skin cells even after repeated peels. The hydrogel adhesive initially removes dead surface skin cells, the second peel removes viable round cells which may have been loosely adhered to the skin and near exfoliation and the final peel removes fewer of these cells probably because the majority of these cells were likely to have been removed with the second peel.

5.19 Conclusion

Four theories exist to try and explain adhesion: mechanical, electrostatic, diffusion and absorption. However no one theory fully explains the totality of the adhesion phenomenon. Bioadhesives must possess physical properties of sufficient flexibility to conform to the contours of the adherend and possess a sufficiently high molecular weight and functional groups to promote hydrogen bonding. The need for a method to test bioadhesion was established and the rolling ball test, the probe tack test and the peel test have been examined. The 180 and 90 degree peel test is of particular interest. The 90 degree peel test proved to be better than the 180 degree peel test for assessing the adhesives tested. This is because the 180 degree peel test gave a stop start effect which was enhanced by the angle of peel.

Four substrates were tested to determine their potential to be used as a skin alternative for testing adhesives. Two skin substitutes failed to be effectively utilised to test the peel strength of NaAMPS as an adhesive due to the inability of the adhesive to adhere to them. The latex model provided reproducible results but the peel strength was very low. Both the metal plate and the skin on the arm of a volunteer proved to be the best method for testing peel strength. The main reasons for having an alternative to skin was to reduce subject to subject variability and to avoid the possibility of inducing an inflammatory response. However, skin still remains the best substrate on which to test skin adhesives as the effects of lipids in the skin and the salts in sweat cannot be reproduced in the models tested.

Gel thickness was also found to be an important factor in determining peel strength and should be considered when comparing peel strengths where an increase in thickness may result in an increased peel strength. Altering the gel thickness may enable the peel strengths to be manipulated to prevent pain or to increase adhesion of certain hydrogel adhesives.

The peel strength of the adhesives tested appears to correlate with skin damage. Adhesives with lower peel strength only peels off dead skin cells. As the peel strength increases more dead cells and hair is removed until eventually live cells are removed. Adhesives adhered to the skin for longer periods of time have an increased chance of removing live cells.

Chapter 6

The Influence of Ionic Monomers and Hydrophobic Polymers on Peel Strength, Surface Free Energy and Dynamic-Mechanical Properties

6.1 Expectations of a skin adhesive hydrogel

Bioadhesives must be able to adhere to the skin for between 24 hours and 7 days depending on their use, and on removal must not cause trauma to the skin or leave any residue. The hydrogel should remain adhesive after removal as repositioning on the body may be required. Additionally, it would be beneficial if the bioadhesive looked aesthetically pleasing.

The adhesives should have a high potential EWC, but should not be fully hydrated, to maintain the gel's affinity for water. A low interfacial tension is required to enable the gel to adhere to the skin, and polar external groups are favoured for water uptake. The proportion of water and the control of the hydrodynamics is vital for bioadhesion hence the role of the polymer structure in controlling water binding is an essential element in the understanding and design of bioadhesive hydrogels. These hydrogels must also have a high mechanical strength to enable them to remain cohesive should the gels require removal and repositioning on the body. This may be achieved by the addition of a water soluble interpenetrant polymer. HPMC, gum karaya, gum locus bean and gum xanthan have been used in earlier patents to enhance strength[59,61,83]. Bioelectrodes furthermore are required to be conductive and ionic monomers are often employed for this purpose. These are just a few of the criteria which must be met to produce a good adhesive.

This chapter investigates the ionic monomers showing the potential to produce a good skin adhesive hydrogels and considers the effect of these ionic monomers and the addition of hydrophobic polymers on peel strength, dynamic mechanical properties, tack and surface free energy in attempt to understand what properties make a gel a good skin adhesive.

6.2 Investigation of Ionic Monomers for Skin Adhesive Gels

Seven ionic monomers were examined to determine their skin adhesive properties in a simple system of glycerol, water, photoinitiator and cross-linker. The ionic monomers were chosen for their hydrophilic properties and they were NaAMPS, SPA, SPE, SPI, SPM, SPP and SPV. Their structures are shown in chapter 2, section 2.2 and all

monomers consist of functional side groups attached to a polymerisable double bond. SPA has a sulphonate group which is an important as a water binding group and also a carbonyl group which may interact with water to a lesser extent by hydrogen bonding. SPM differs from SPA by the presence of a backbone methyl group while SPI contains two sulphonate groups and two carbonyl groups. SPE is a zwitterion, possessing both a positive and negative charge in the same chain. SPE has a charged quaternary nitrogen and a sulphonate group. SPP is like SPE with an additional methyl group. NaAMPS has a sulphonate group linked to the double bond by an amide group. The components were mixed together and passed under UV light seven times to allow polymerisation to occur. The photoinitiator Irgacure 184 and cross-linker Ebacryl II were mixed at a ratio of 3:10 respectively. The formulations produced are shown below:

NaAMPS (%)	SPA (%)	SPE (%)	SPI (%)	SPM (%)	SPP (%)	SPV (%)	Glycerol (%)	Water (%)	PI/XL (%)
40.5	0	0	0	0	0	0	31	28.5	0.3
0	40.5	0	0	0	0	0	31	28.5	0.3
0	0	40.5	0	0	0	0	31	28.5	0.3
0	0	0	40.5	0	0	0	31	28.5	0.3
0	0	0	0	40.5	0	0	31	28.5	0.3
0	0	0	0	0	40.5	0	31	28.5	0.3
0	0	0	0	0	0	40.5	31	28.5	0.3

Table 6.1 Compositions (w/w) of gels used to investigate cohesion and adhesion.

6.2.1 The Quality of Gel Produced from Different Ionic Monomers

The quality of the gels in terms of cohesiveness and adhesiveness were investigated. Gels made from ionic monomer NaAMPS, were found to be of far superior quality in comparison to gels made from the ionic monomers SPE, SPI, SPM, SPP and SPV. Gels made from the ionic monomer SPA produced a good quality gel which was more adhesive, but less cohesive than gels made from NaAMPS. Unfortunately the other ionic monomers produced a viscous liquid rather than a gel when used as the sole monomer, despite repeated UV exposure and adequate levels of both photoinitiator and cross-linker. This highlights an important point. In order for this "open face" polymerisation of aqueous gels, to be successful, the polymerisation rates of monomer must be

acceptably high. Otherwise, water loss and oxygen inhibition become increasingly important.

6.3 Sodium 2-acrylamido 2-2 Methyl Propane Sulfonic Acid (NaAMPS) Hydrogels

Gels were produced in which seventy percent of the ionic monomer in the system was present as NaAMPS since NaAMPS produced good quality gels in terms of both cohesiveness and adhesiveness. The remaining thirty percent of the ionic monomer in the system was present either as SPA, SPE, SPI or SPM to try to incorporate further properties into a good quality NaAMPS gel. It was thought that a high percent of NaAMPS in the monomer mixture would help the monomer solution polymerise faster and more efficiently. The formulations tested are shown below in table 6.2.

NaAMPS (%)	SPA (%)	SPE (%)	SPI (%)	SPM (%)	Glycerol (%)	Water (%)	PI/XL (%)
28.1	12.4	0	0	0	31	28.5	0.3
28.1	0	12.4	0	0	31	28.5	0.3
28.1	0	0	12.4	0	31	28.5	0.3
28.1	0	0	0	12.4	31	28.5	0.3

Table 6.2 Compositions (w/w) of gels containing NaAMPS used to investigate cohesion and adhesion.

6.3.1 Comparison of the Cohesion and Adhesion of Gels Comprised of NaAMPS

All of the gels tested were moderately cohesive and adhesive, however, they all possessed a large amount of monomer residue on their surface except for SPA which had virtually no residue. Peel tests were performed on all gels. Unfortunately these results were unreliable due to the large amounts of residue which affected adhesion and therefore they are not shown here. The exception was the gel containing SPA and the peel results are shown later in this chapter.

It was thought that the gels may not polymerise as they contained too much glycerol. The gels were reproduced using the same formulae but this time the glycerol was

omitted. No residue was found but the adhesion was also lost. The original system contains a large amount of plasticiser in the form of glycerol and water. A high amount of plasticiser is required to allow chain movement. Unfortunately when glycerol was incorporated into the polymer mixture containing ionic monomers SPI, SPE or SPM, then poor non-cohesive gels were formed. Increasing the amount of plasticiser in the form of water, would not be a viable alternative because when too much water is present in the system then there is a decreased affinity for water, causing a reduction in adhesion. Therefore SPI, SPM and SPE were not investigated further in this system for producing adhesive gels.

6.4 Addition of Acrylic Acid to the NaAMPS and Ionic Monomer Gels

Acrylic acid was added to the polymer solution in order to increase the water binding potential of the gel and reduce the residue on the gel surface by increasing the hydrogen bonding and hydrophilic potential of the gel. The compositions tested are shown in the table below.

NaAMPS (%)	SPA (%)	SPE (%)	SPI (%)	SPM (%)	Glycerol (%)	Water (%)	Acrylic Acid (% added)	PI/XL (%)
28.1	12.4	0	0	0	31	28.5	4	0.3
28.1	0	12.4	0	0	31	28.5	4	0.3
28.1	0	0	12.4	0	31	28.5	4	0.3
28.1	0	0	0	12.4	31	28.5	4	0.3

Table 6.3 Compositions (w/w) of gels with added acrylic acid used to investigate cohesion and adhesion.

6.4.1 The effects of Acrylic Acid on NaAMPS-Based and Other Ionic Monomer Gels

The gels (table 6.3) were reproduced with 4% acrylic acid added, but in preliminary experiments only SPA showed a detectable reduction in surface residue and in this case only trace amounts of residue could be detected. Therefore SPA was the only ionic monomer chosen for further investigation with NaAMPS and a range of percentages of acrylic acid added.

6.5 Photoinitiator and Cross-linker Requirements for NaAMPS and SPA Hydrogels

The photoinitiator Irgacure 184 and the cross-linker Ebacryl II was mixed in a ratio of 3:10 respectively. A high percentage of photoinitiator and cross-linker was previously used to ensure that the polymerisation did not foil due to a lack of photoinitiator and cross-linker. However, SPA and NaAMPS can be successfully polymerised using lower levels of photoinitiator and cross-linker and the optimum level required was determined prior to further investigations. The gels should have the lowest amount of photoinitiator and cross-linker amount possible to maximise the potential affinity for water but without compromising mechanical strength.

NaAMPS (%)	SPA (%)	Glycerol (%)	Water (%)	DM 137 (% added)	PI/XL (%)
28.1	12.4	31	28.5	0	0.30
28.1	12.4	31	28.5	0	0.25
28.1	12.4	31	28.5	0	0.20
28.1	12.4	31	28.5	0	0.15
28.1	12.4	31	28.5	0	0.10
28.1	12.4	31	28.5	0	0.05

Table 6.4 Compositions (w/w) of gels used to determine the optimum quantities of photoinitiator and cross-linker.

6.5.1 The Optimum Amount of Photoinitiator and Cross-linker

When the percentage of photoinitiator and cross-linker mixture incorporated into the formulation was too high, the adhesion was reduced. This is because the retractive forces exerted by the cross-links restrict water uptake and expansion, and also reduce flexibility and therefore compliance with the tissue surface. The percentage of the PI/XL mixture is too low then the gel does not form a strong network, is less cohesive and appears more in the form of a viscous liquid than a gel, even after repeated exposure to UV. The optimum value was found to be 0.1% of the photoinitiator and cross-linker added to the monomer mixture on the basis of empirical observation. This value is low

in comparison to the other combinations of ionic monomers tested which contained SPM and SPE.

6.6 Investigation of NaAMPS Hydrogels for Adhesion and Cohesion

The NaAMPS gel was found to be of good quality and very adhesive but improvements were imperative to produce a good cohesive gel without reducing adhesiveness. Reducing the residue on the surface of the gel and enhancing adhesion was expected to increase gel cohesion and reduce potential toxicity. Surface residue should also be reduced to enable the product gel to be stored without leakage. The effects of adding acrylic acid in an attempt to increase water binding potential and poly (ethylene-co-vinyl acetate) emulsion (DM 137), to increase adhesiveness and strength, was subsequently investigated for both NaAMPS and NaAMPS:SPA containing gels. The gels were tested using the 90 degree peel test on skin to determine how difficult it was to remove the adhesive following attachment to an adherend (skin), the goniometer technique was used to determine the contact angles of the gels to define the surface free energy of the gel and observe if a specific surface energy could be used to predict adhesion, while the rheometer was used to enable the dynamic mechanical properties of the gel to be determined.

Dynamic mechanical analysis provides quantitative information on the viscoelastic and rheological properties of a material by measuring the mechanical response of a sample as it is deformed under periodic stress (or strain). When the dynamic mechanical behaviour of hydrogels are investigated, the three main parameters that are determined are G', G'' and tan delta. G' is the elastic or storage modulus and provides information on the elastic properties of the gel, G'' is the imaginary, viscous or loss modulus providing information on the viscous, liquid properties of the gel and tan delta, also known as the dampening factor, provides an indication of G''/G', the ratio of the energy dissipated as heat to the maximum energy stored in the material during one cycle of oscillation[84,85].

The dynamic mechanical properties of a series of gels were tested at 37 degrees Celsius, body temperature, to give an indication of the rheological properties on the skin. The tests were performed at a frequency range of 1-100 radians per second. A suitable range

which was determined by an amplitude sweep. If the amplitude recorded was too high irreversible damage to the gel would be caused and invalidate the results.

6.6.1 The Percentage of Components Required to Give Adhesive and Cohesive Gels

Recent patents[86-89] enable us to estimate the percentages of NaAMPS, water and glycerol required to produce an adhesive gel. No patent, however, clearly defines the upper and lower limits of these components to produce both adhesive and cohesive gels, in particular using only 3 main components. A series of simple gels containing NaAMPS, glycerol and water were produced to distinguish these parameters and the gel compositions and properties are shown in the triangular graph figure 6.1 and appendix 4. The triangular graph displays clearly the acceptable range of compositions that give good adhesion and cohesion. The perimeter of the white triangle shows the lower limits of acceptable compositions for adhesive and cohesive gels, with the centre revealing the best compositions for the components used.

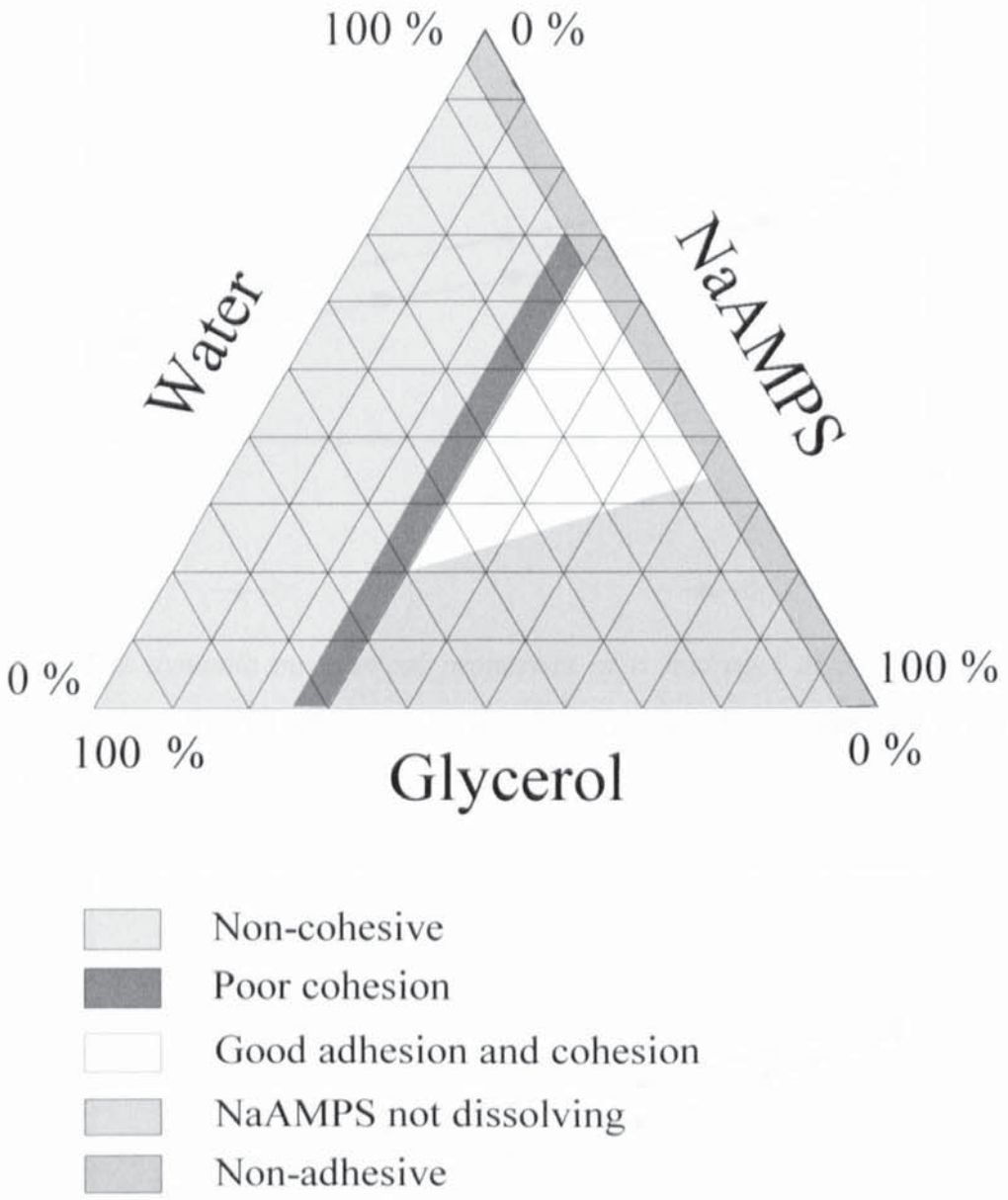


Figure 6.1 A triangular graph revealing the properties created from various monomer, glycerol and water compositions (w/w).

6.6.1.2 Dynamic Mechanical Properties of NaAMPS Gels

The gels that demonstrated good adhesion and cohesion properties were subject to dynamic mechanical testing to define the rheological properties that comprised a good pressure sensitive adhesive.

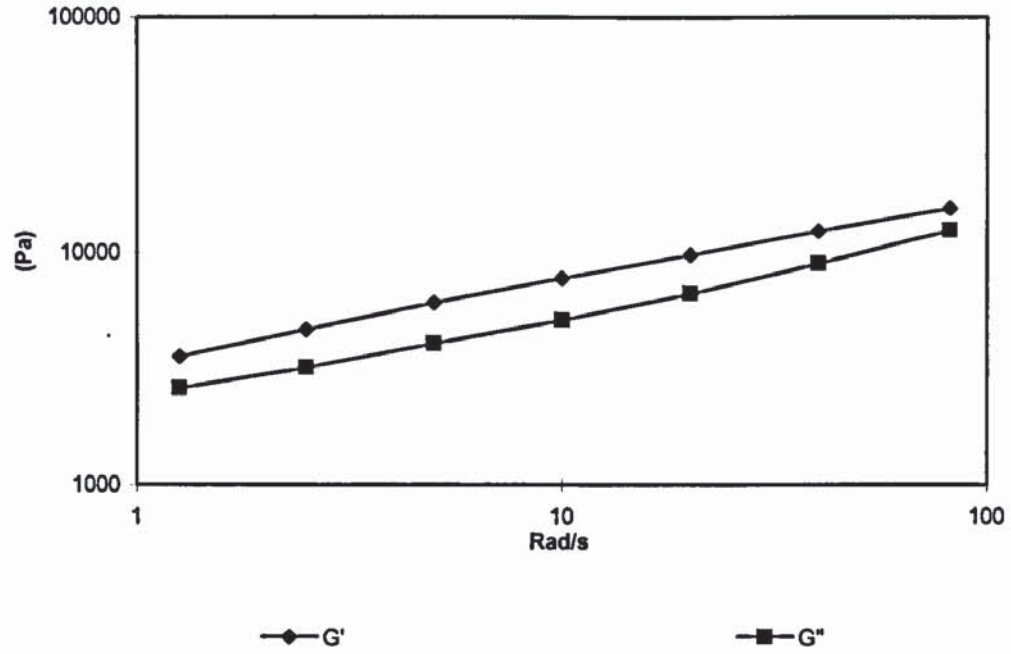


Figure 6.2 The dynamic mechanical properties of a hydrogel at 37 degrees Celsius consisting of (w/w) 40% NaAMPS, 30% glycerol, 30% water and 0.1% added PI/XL.

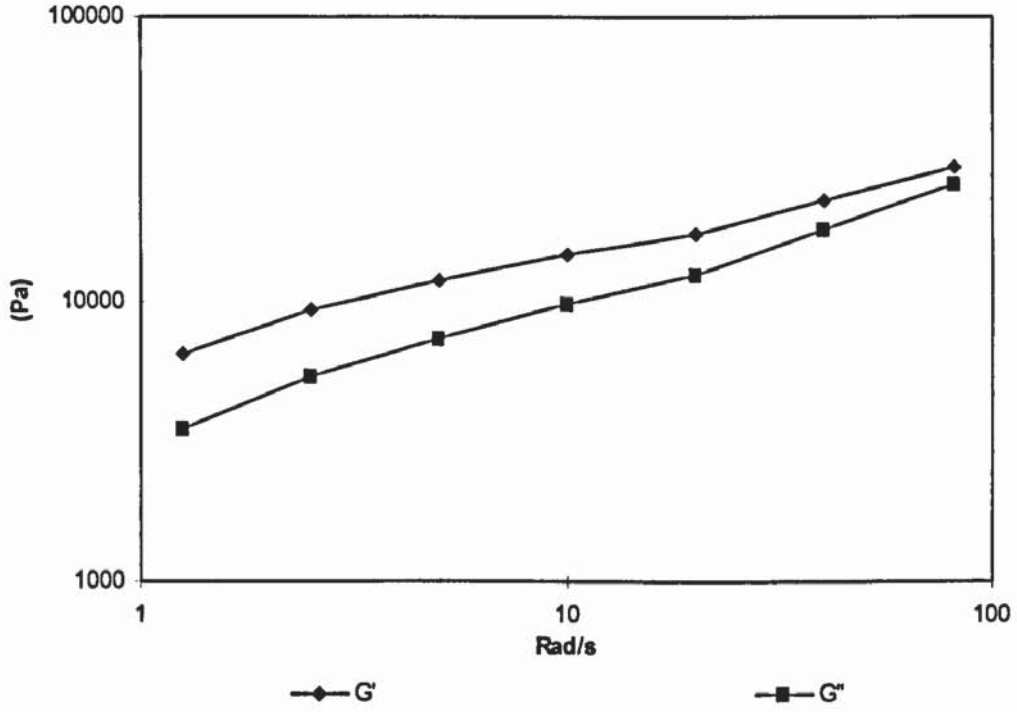


Figure 6.3 The dynamic mechanical properties of a hydrogel at 37 degrees Celsius consisting of (w/w) 40% NaAMPS, 20% glycerol, 40% water and 0.1% added PI/XL.

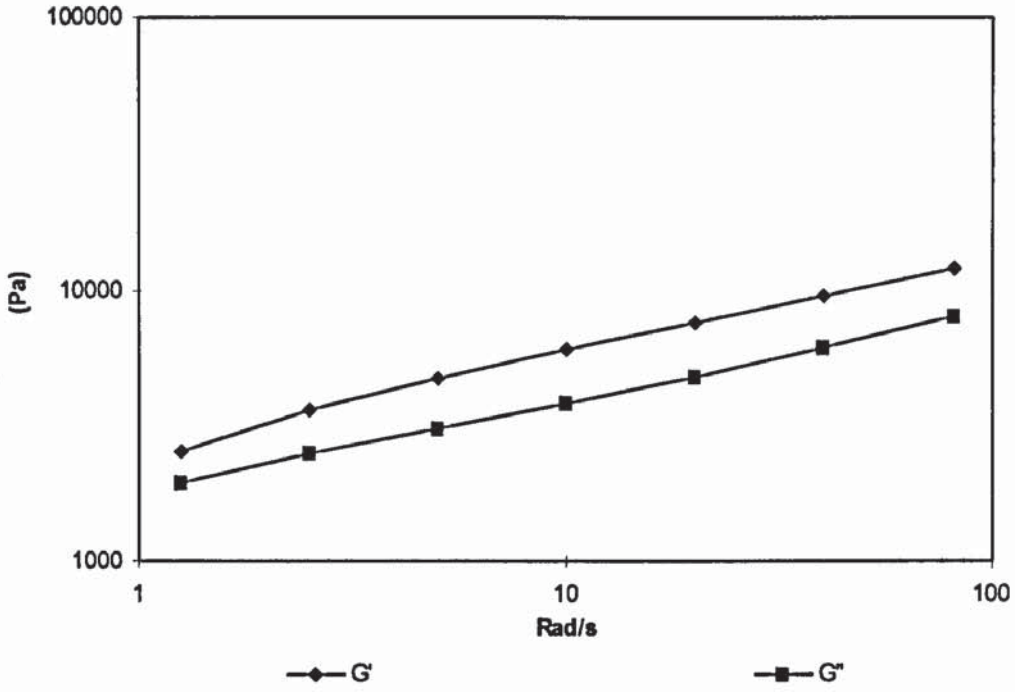


Figure 6.4 The dynamic mechanical properties of a hydrogel at 37 degrees Celsius consisting of (w/w) 40% NaAMPS, 31% glycerol, 29% water and 0.1% added PI/XL.

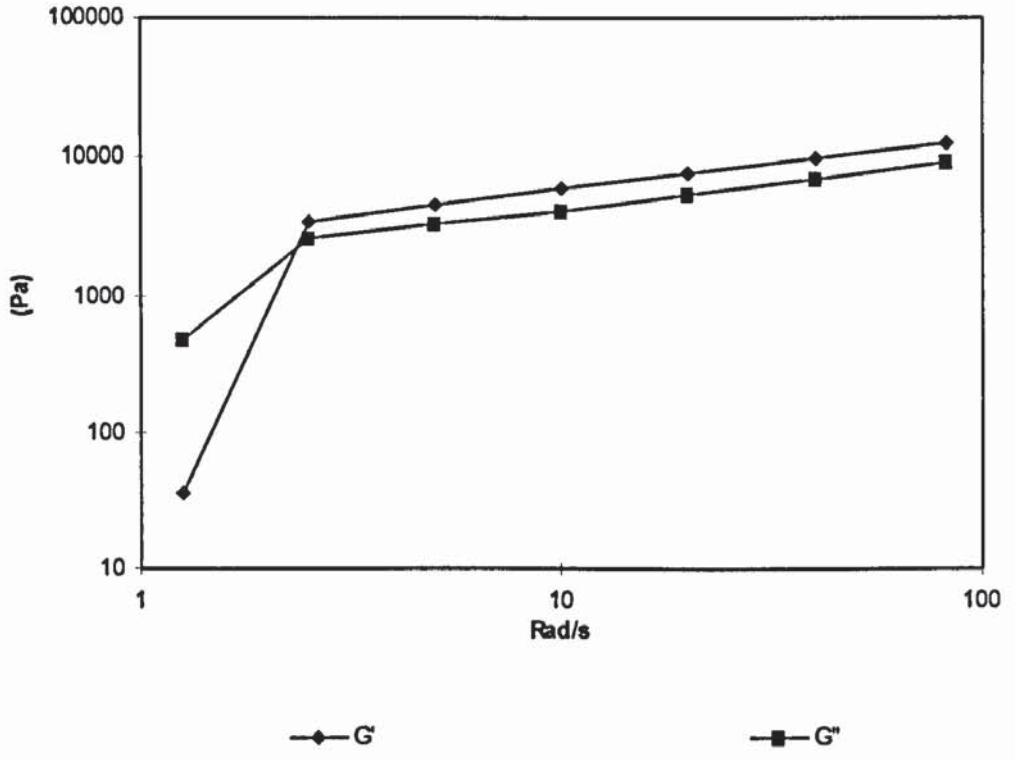


Figure 6.5 The dynamic mechanical properties of a hydrogel at 37 degrees Celsius consisting of (w/w) 37% NaAMPS, 29% glycerol, 34% water and 0.1% added PI/XL.

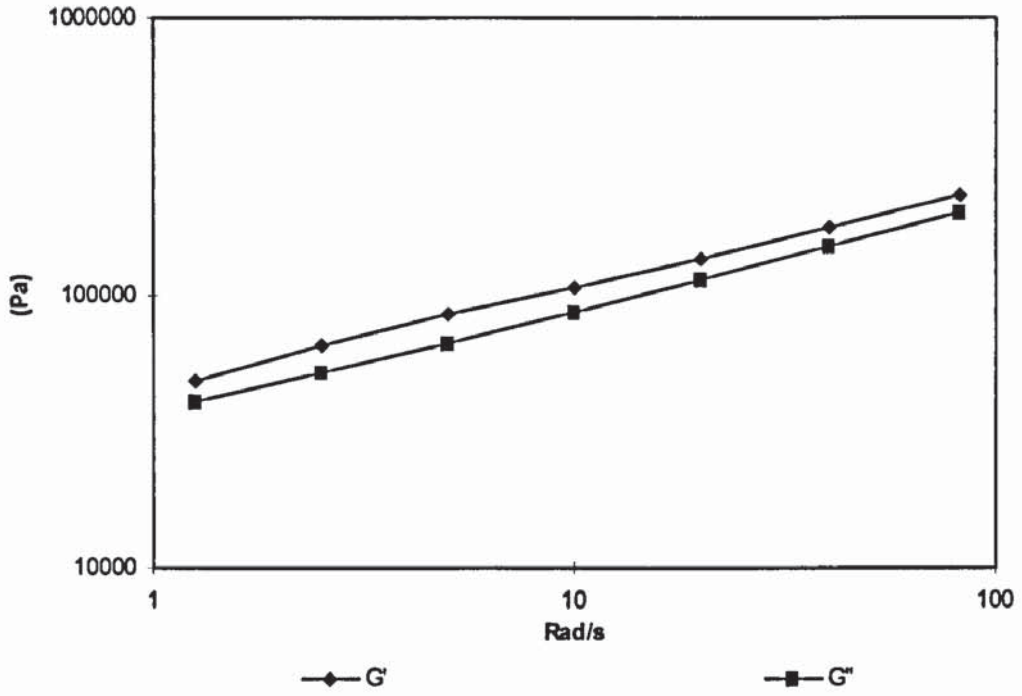


Figure 6.6 The dynamic mechanical properties of a hydrogel at 37 degrees Celsius consisting of (w/w) 50% NaAMPS, 10% glycerol, 40% water and 0.1% added PI/XL.

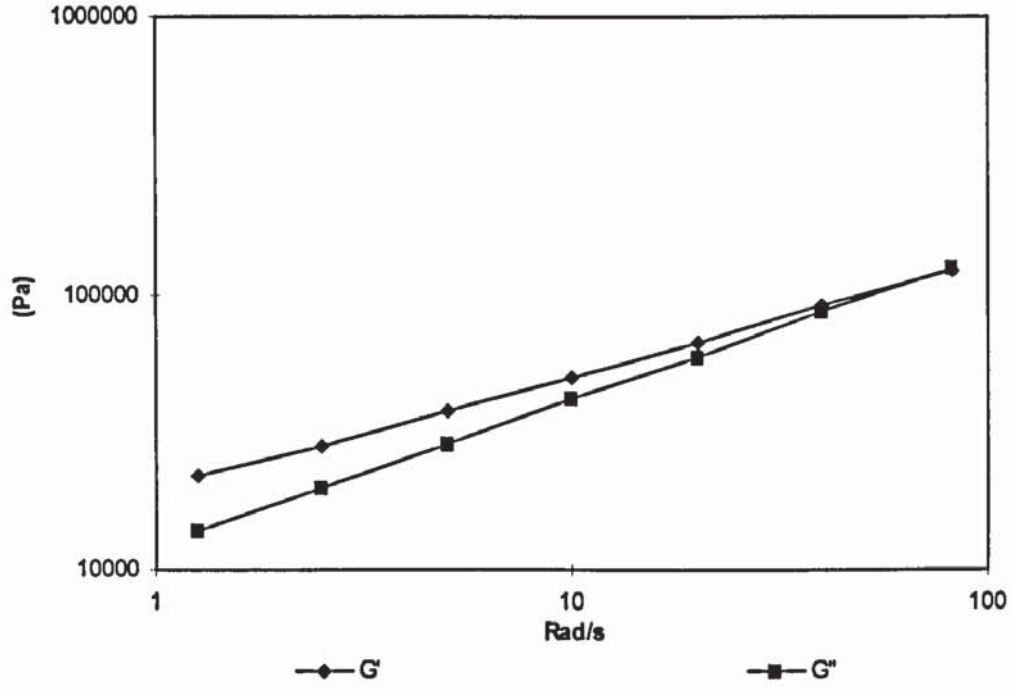


Figure 6.7 The dynamic mechanical properties of a hydrogel at 37 degrees Celsius consisting of (w/w) 40%NaAMPS, 10% glycerol, 50% water and 0.1% added PI/XL.

G', the elastic modulus should be high for a good pressure sensitive adhesive and should also be greater than G'' the viscous modulus, otherwise the material would be more viscous than elastic and therefore would not exhibit good cohesion. Tests of the gels indicate that in the region of 10^3-10^5 Pa, cohesion was good (figure 6.2-6.5), with 10^4-10^5 being preferred (figure 6.6 and 6.7). Below 10^3 Pa the gels were too weak and non-cohesive. No gels were produced above 10^5 Pa from the compositions tested. However, if the gels become too rigid, they may not conform to the skin well, and as a result, may become less adhesive.

It was noted that the higher the percentage of NaAMPS used the better the cohesion shown by increased G' (figure 6.6 and 6.7), with water being preferred over glycerol to enhance cohesive strength (figures 6.2, 6.3, 6.6 and 6.7). The water gives greater cohesive strength to the gel due to the additional hydrogen bonding it donates and the ability to free the chains to enable intermolecular interaction between polymer chains.

6.6.1.3 Determination of the Relative Humidity of a NaAMPS Hydrogel

Dynamic Vapour Sorption was used to determine the relative humidity of a NaAMPS hydrogel, an important property when considering the suitability of the gel for storage and processing. The DVS rapidly measures uptake and loss of moisture by flowing a carrier gas, nitrogen, at specified relative humidity. This was done at 37 degrees Celsius to determine the effect of water uptake and loss at body temperature.

The gel consisted of 40% NaAMPS, 28% Glycerol and 32% water and was 1cm in diameter and 2 mm in depth. A sample any larger may have been too heavy for the sensitive Cahn microbalance.

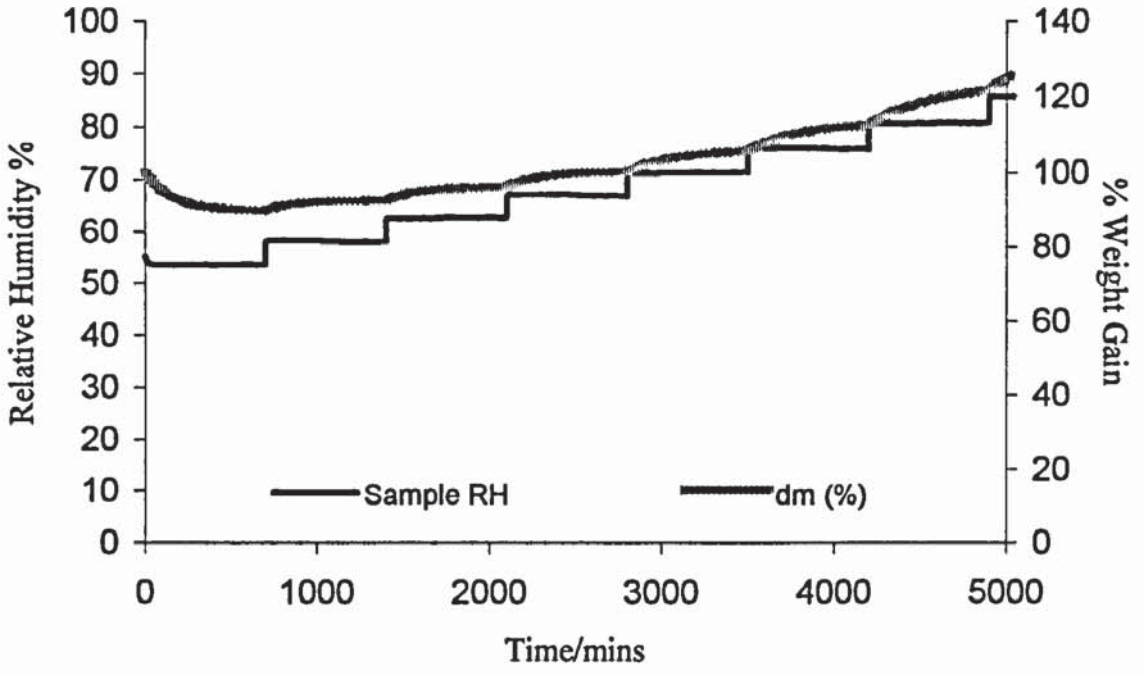


Figure 6.8 The Dynamic Vapour Sorption properties of a NaAMPS gel *(40% NaAMPS, 28% glycerol and 32% water) at 37 degrees Celsius.*

The graph shows kinetics of moisture sorption on a NaAMPS hydrogel at 37 degrees. The materials equilibrium humidity is 65%. At each change in humidity the gel is allowed to equilibrate shown by the plateau. The uptake of moisture is an important factor to consider for long storage periods, and moisture uptake should be kept to a minimum to prolong shelf life. This experiment was performed to demonstrate that the DVS can be used to accurately study the kinetics of moisture sorption and to obtain the relative humidity of the sample.

6.6.2 Components Used to Investigate the effect of Acrylic Acid on NaAMPS Gels

NaAMPS (%)	Glycerol (%)	Water (%)	Acrylic Acid(% added)	PI/XL(%)
40	28	32	0	0.1
40	28	32	5	0.1
40	28	32	10	0.1

Table 6.5 Compositions (w/w) of gels used to investigate the increasing percentage of acrylic acid.

6.6.2.1 The Addition of Acrylic Acid to a NaAMPS Hydrogel on Surface Free Energy and Peel Strength

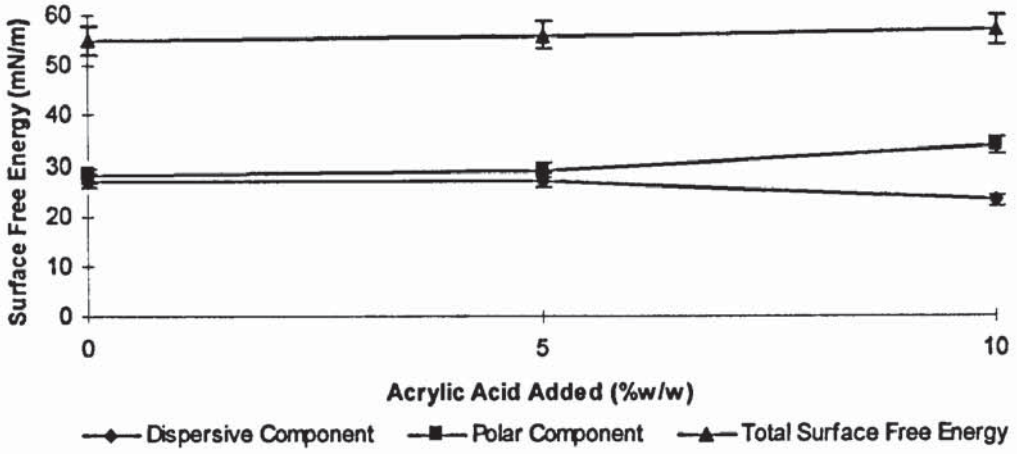


Figure 6.9 NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with increasing percentage of acrylic acid.

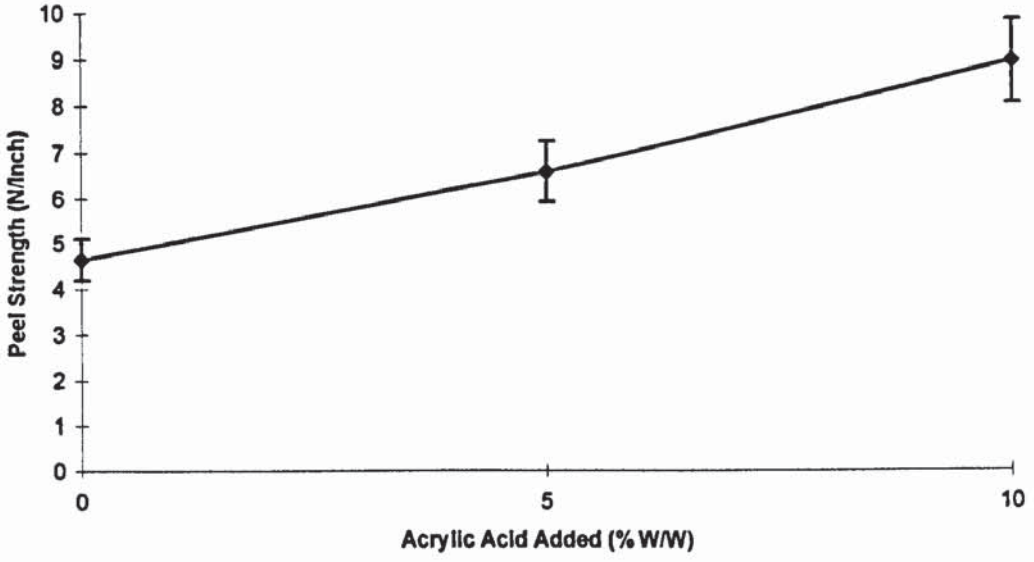


Figure 6.10 Peel strength of NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with increasing percentage of acrylic acid.

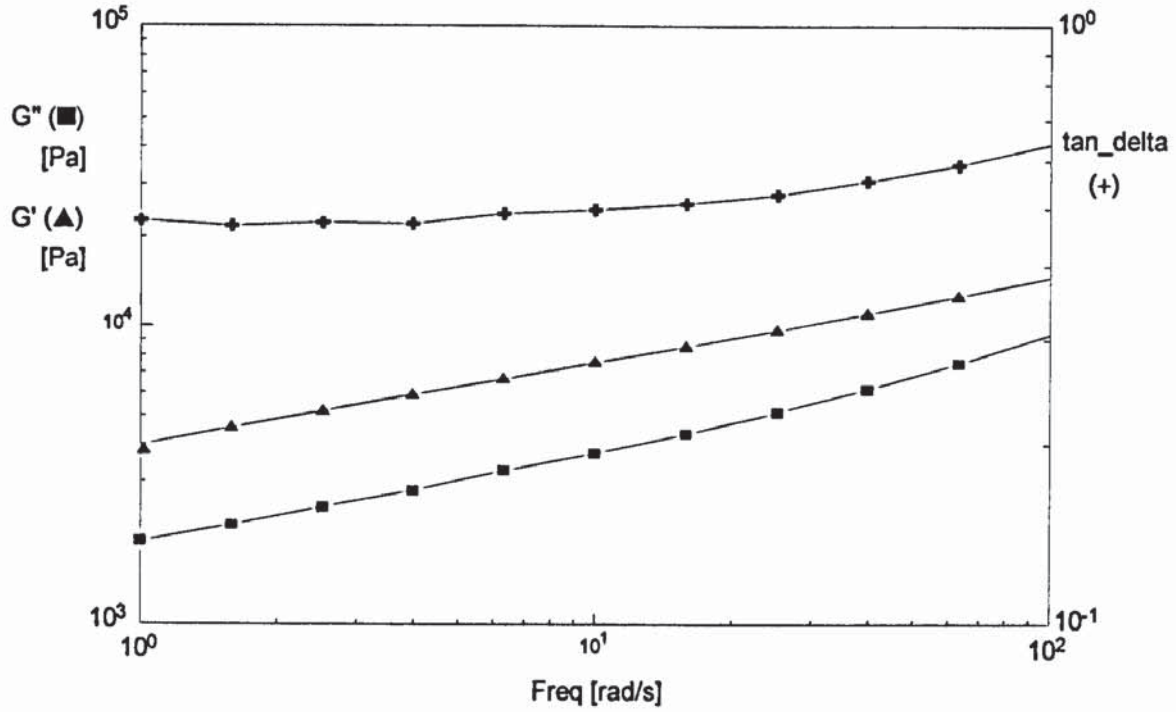


Figure 6.11 The rheological properties of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) at 37°C 1-100 rad/s.

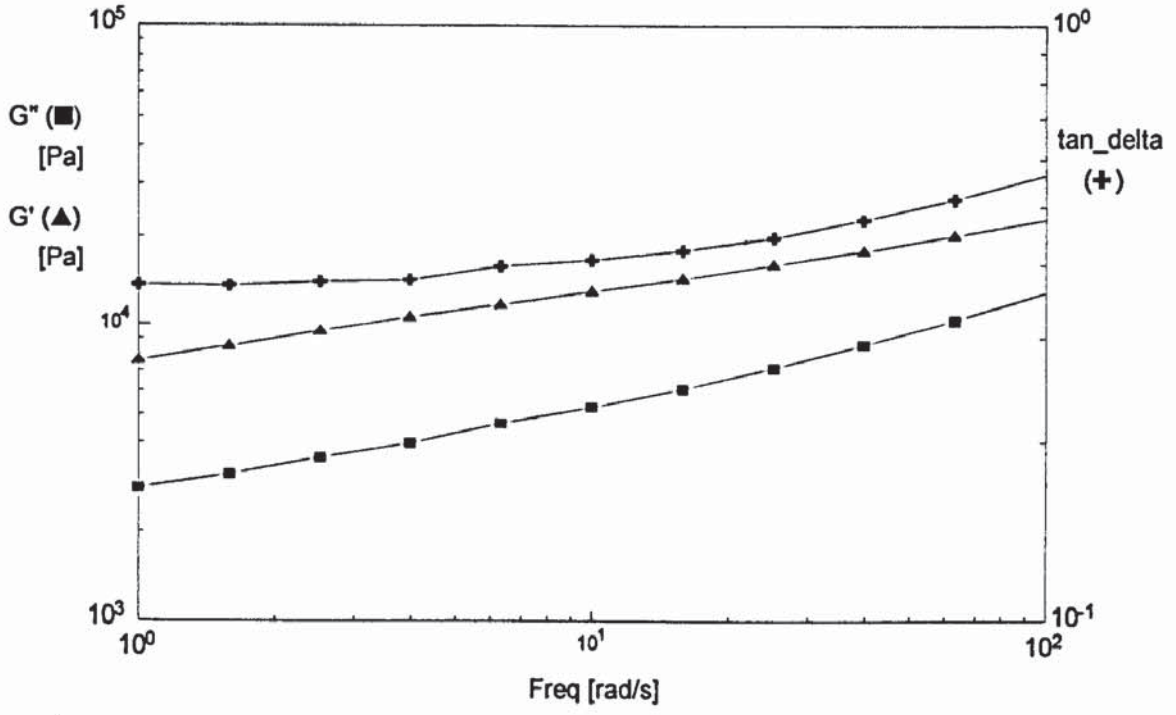


Figure 6.12 The rheological properties of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with 5 % added acrylic acid at 37°C 1-100 rad/s.

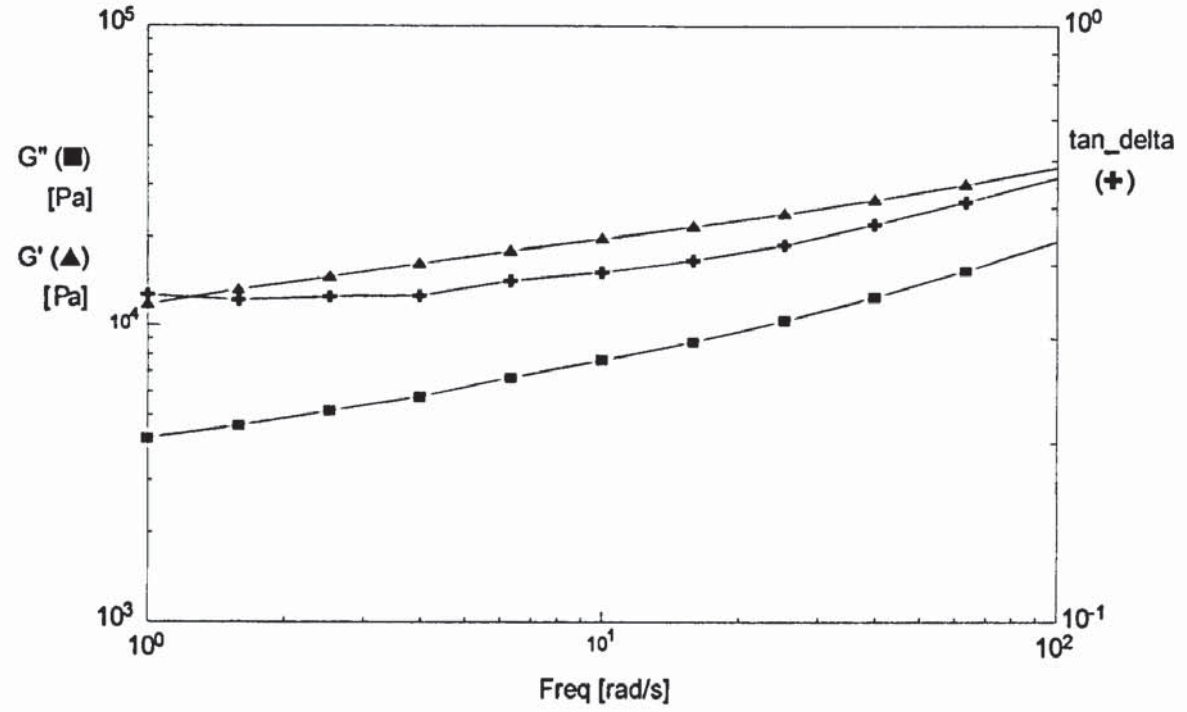


Figure 6.13 The rheological properties of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with 10% added acrylic acid at 37°C 1-100 rad/s.

6.6.2.2 The Effect of Acrylic Acid on NaAMPS Gels

The addition of acrylic acid to the system (40% NaAMPS, 28% Glycerol and 32% water) greatly reduces the surface residue, only trace residues could be detected. It can be seen that the peel strength increases as the amount of acrylic acid added increases (figure 6.9), this could be due to the water binding properties of acrylic acid. Whereby, the acrylic acid could be removing the interfacial layer of moisture and holding it within the gel.

The polar component of the gel only increases slightly while the dispersive component decreases just slightly causing the total surface free energy to remain constant (figure 6.10). The acrylic acid appears to act within the gel by increasing intermolecular interactions. The hydroxyl group of the acrylic acid is intermolecular bonding with the amide group and the sulphonate group of NaAMPS. The total surface free energy

remains constant because the polar acrylic acid is held tightly within the gel. There is a slight decrease in the dispersive component at high acrylic acid values. This latter effect may arise because the centre of the gel had reached its upper limit of acrylic acid uptake and a small amount has reached the surface.

The gels studied followed a similar trend in dynamic mechanical properties, that is, that at a frequency of 1 rad/s there is a low G' and low G'' which increase as the frequency increases. Tan delta only increases slightly with increasing frequency. This demonstrates that the viscoelastic properties are increasing with frequency. When comparing a series of gels, G' at 1 rad/s and 100 rad/s gives an indication of the performance of the hydrogel in terms of cohesive strength, the higher the G' the better the cohesive strength. The gels tested provide information on the viscoelastic properties of such gels when acrylic acid is added, a property which is very important for gels which may be repositioned on the body and are expected to be durable. G' increased greater than G'' at a frequency of 1-100rad/s showing that the samples tested were more elastic than viscous and became more elastic and less viscous as more acrylic acid was added.

The addition of 5% acrylic acid (figure 6.12) causes an increase in G' and G'' compared to the gel without acrylic acid (figure 6.11) and this increase is further enhanced when 10 % acrylic acid is added (figure 6.13). This indicates that addition of acrylic acid to the gel causes an increase in the cohesive strength of the adhesive. The later effect may be caused by the intermolecular interaction between polymer chains within the gel which may serve to reduce chain slippage and bind water more tightly.

6.6.2.3 Comparison of Acrylic Acid, Acrylamide and N-Iso-Propyl Acrylamide

Acrylic acid, acrylamide and N-iso-propyl acrylamide were all integrated into 3 separate NaAMPS gels to ascertain their effect on peel strength. Acrylic acid had been shown previously to increase the cohesive strength and increase adhesive strength of the resultant gels, due to increased intermolecular bonding within the gel and removal of interfacial water. Acrylamide differs from acrylic acid by an amide group in place of a hydroxyl group, while N-iso-propyl acrylamide has both a propyl and amide group

instead of a hydroxyl group. There structures are shown in chapter 2. The gel compositions are shown below in table 6.6.

NaAMPS (%)	Glycerol (%)	Water (%)	Acrylic Acid (% added)	Acrylamide (% added)	NIPA (% added)	PI/XL (%)
40	28	32	5	0	0	0.1
40	28	32	0	5	0	0.1
40	28	32	0	0	5	0.1

Table 6.6 Compositions (w/w) of gels used to investigate the properties acrylic acid, acrylamide and N-isopropyl acrylamide exert on NaAMPS (40% NaAMPS, 28% glycerol and 32% water) gels.

6.6.2.4. The effect of Acrylic Acid, Acrylamide and N-Iso-propyl acrylamide on Peel Strength

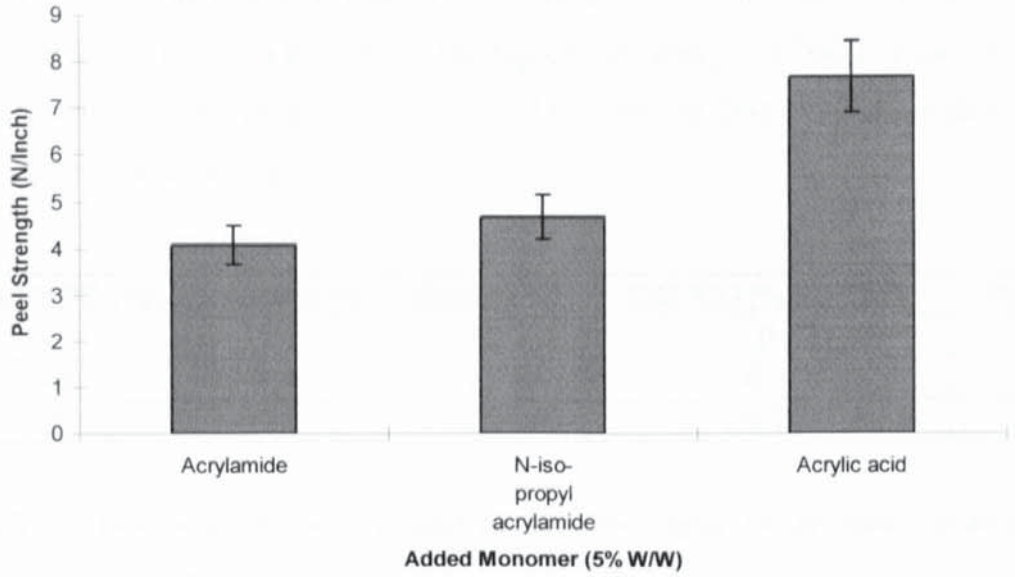


Figure 6.14 The effect of Acrylic Acid, Acrylamide and N-Iso-propyl acrylamide on Peel Strength of a NaAMPS gel (40% NaAMPS, 28% glycerol and 32% water).

The addition of acrylic acid to a NaAMPS gel appears to increase the peel strength more than the addition of acrylamide or N-iso-propyl acrylamide. The hydroxyl group may be better at removing interfacial water than the amide group, which is more likely to hydrogen bond with itself than with water, and may promote more hydrogen bonding (figure 6.14). The hydroxyl group is more polar and less bulky than the amide group and may be better at intermolecular bonding. N-iso-propyl acrylamide appears to enhance skin adhesion presumably due to its hydrophobic groups interacting with the hydrophobic skin.

6.6.3 Components Used to Investigate the effect of DM 137 on NaAMPS Gels

DM 137 is a commercial product which contains 50% polymer, poly (ethylene-co-vinyl acetate), suspended in solution to form an emulsion. The addition of DM 137 was expected to increase the hydrophobic forces on the surface of the gel, which are thought to enhance adhesion. The toughness of the gel would be expected to be enhanced if the polymer acts as an interpenetrant. The components used to produce gels containing DM 137 are shown below in table 6.7. The highest percentage of DM 137 incorporated into the monomer solution was 8.2%, as beyond this amount DM 137 did not dissolve in this specific monomer solution.

NaAMPS (%)	Glycerol (%)	Water (%)	DM 137(% added)	PI/XL(%)
40	28	32	0	0.1
40	28	32	4.1	0.1
40	28	32	8.2	0.1

Table 6.7 Compositions (w/w) of gels used to investigate the presence of an increasing percentage of DM 137.

6.6.3.1 The Effect of DM 137 on the Surface Free Energy and Peel Strength of a NaAMPS Hydrogel

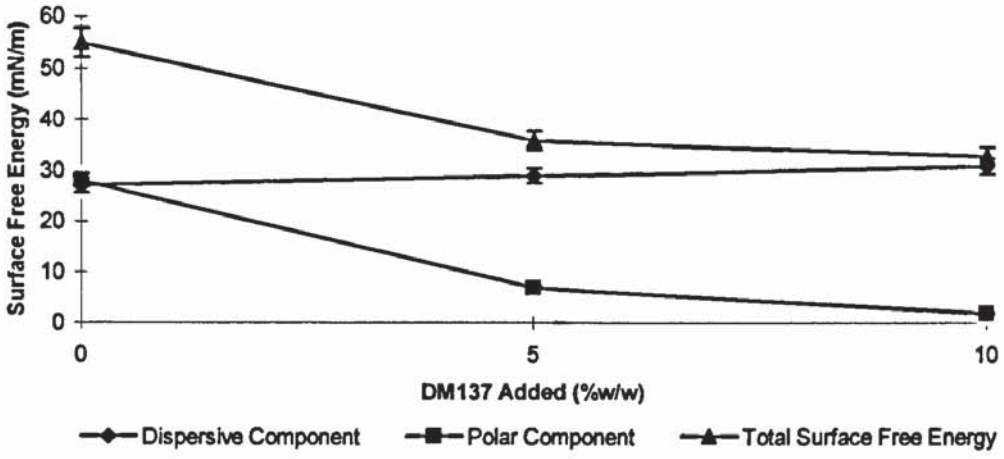


Figure 6.15 The surface free energy of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with increasing percentage of DM 137.

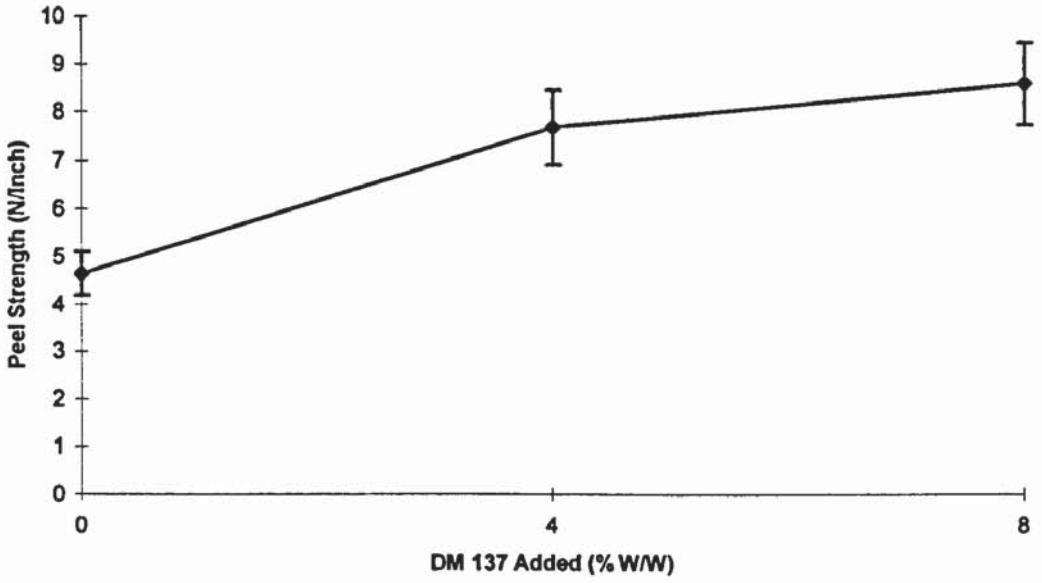


Figure 6.16 Peel Strength of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with increasing percentage of DM 137.

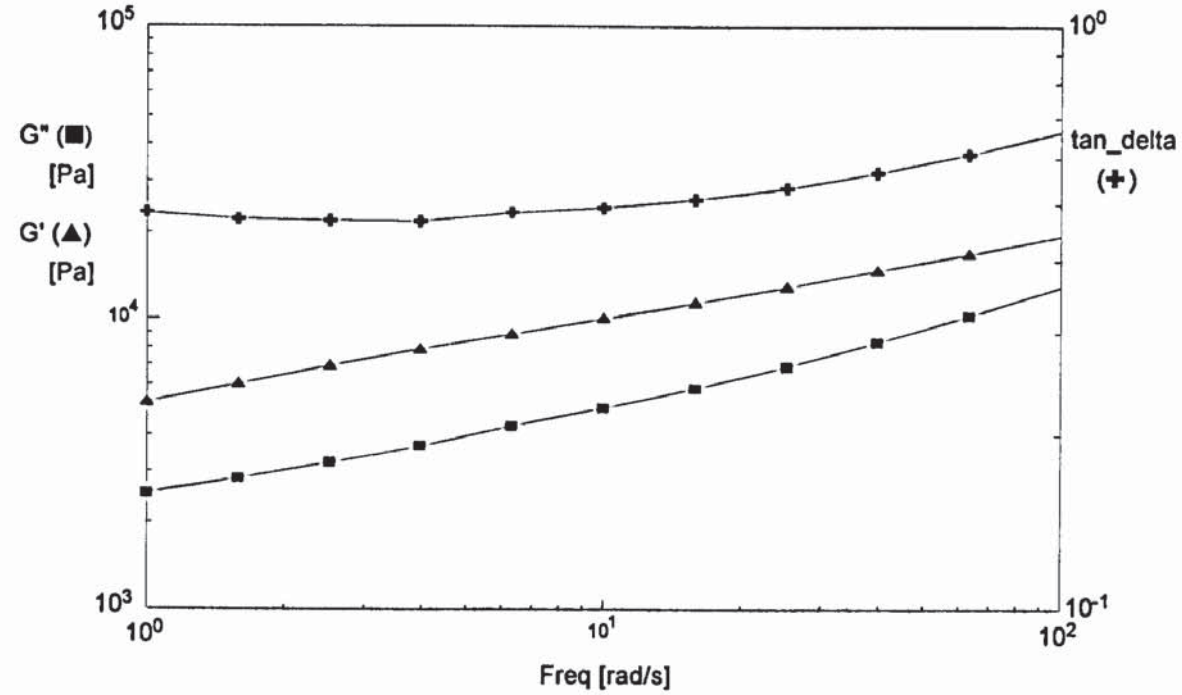


Figure 6.17 The rheological properties of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with 5 % added DM 137 at 37°C 1-100 rad/s.

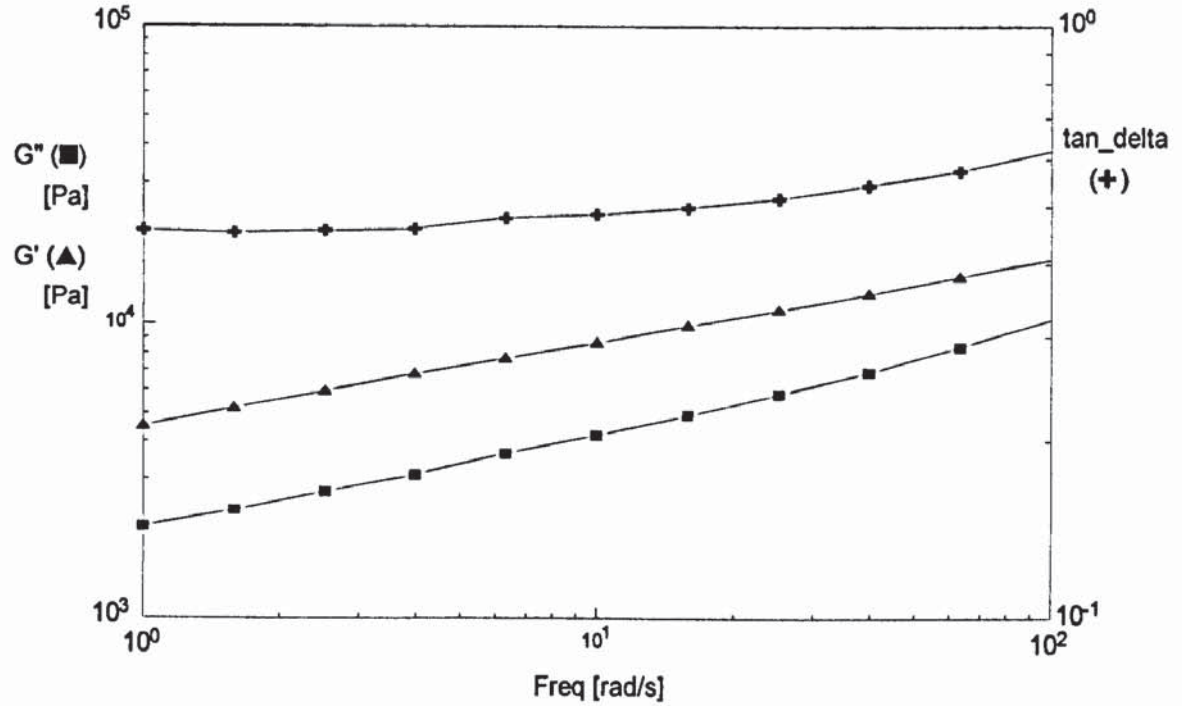


Figure 6.18 The rheological properties of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with 10 % added DM 137 at 37°C 1-100 rad/s.

6.6.3.2 The effect of DM 137 on NaAMPS Gels

The addition of DM 137 to simple NaAMPS hydrogels have been shown and have the effects of a marked increase in peel strength (Fig. 6.16), and reduced the polar component of the gel which in turn reduced the total surface free energy (Fig. 6.15). The increased ratio of dispersive to polar component and the lowered surface free energy, enhanced adhesion due to hydrophobic interactions with the lipids of the skin.

The addition of DM 137 (figure 6.17 and 6.18) gave an increased G' and G'' indicating an improvement in the cohesive strength of the gel compared to the NaAMPS hydrogel alone (Fig. 6.11). However, the addition of 4.1% DM 137 (Fig. 6.17) is sufficient to increase cohesive strength and a further increase the amount of DM 137 to 8.2 % (Fig. 6.18) under similar conditions will not enhance the cohesive strength further. This is because DM 137 acts on the surface of the hydrogel and does not significantly contribute to intermolecular bonding.

6.6.4 Components Used to Investigate the Effect of Acrylic Acid on NaAMPS and DM 137 Gels

NaAMPS (%)	Glycerol (%)	Water (%)	Acrylic Acid (% added)	DM 137 (% added)	PI/XL (%)
40	28	32	0	8.2	0.1
40	28	32	5	8.2	0.1
40	28	32	10	8.2	0.1

Table 6.8 Compositions (w/w) of gels used to investigate the increasing percentage of acrylic acid in a NaAMPS gel (40% NaAMPS, 28% glycerol and 32% water) containing DM 137.

6.6.4.1 The effect of Acrylic Acid on a NaAMPS and 8.2% DM 137 Hydrogel on Surface Free Energy and Peel Strength

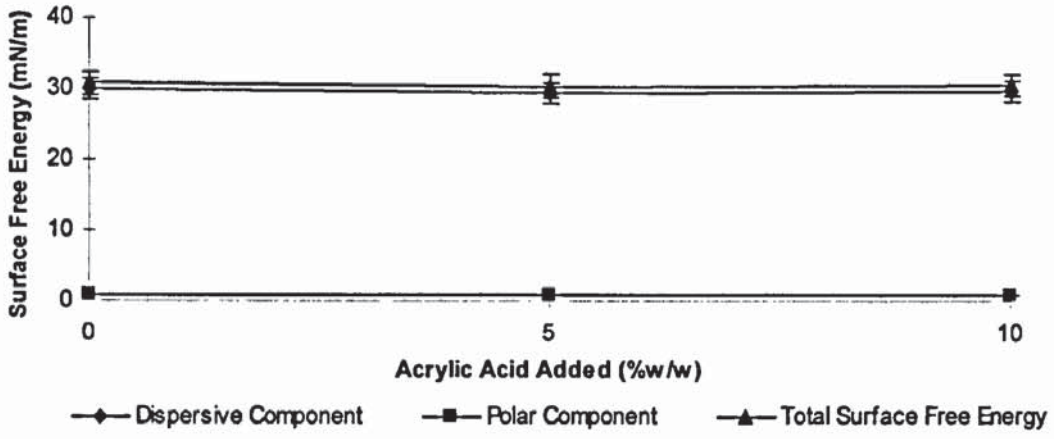


Figure 6.19 NaAMPS gel (40% NaAMPS, 28% glycerol and 32% water) with 8.2% DM 137 hydrogel with increasing percentage of acrylic acid.

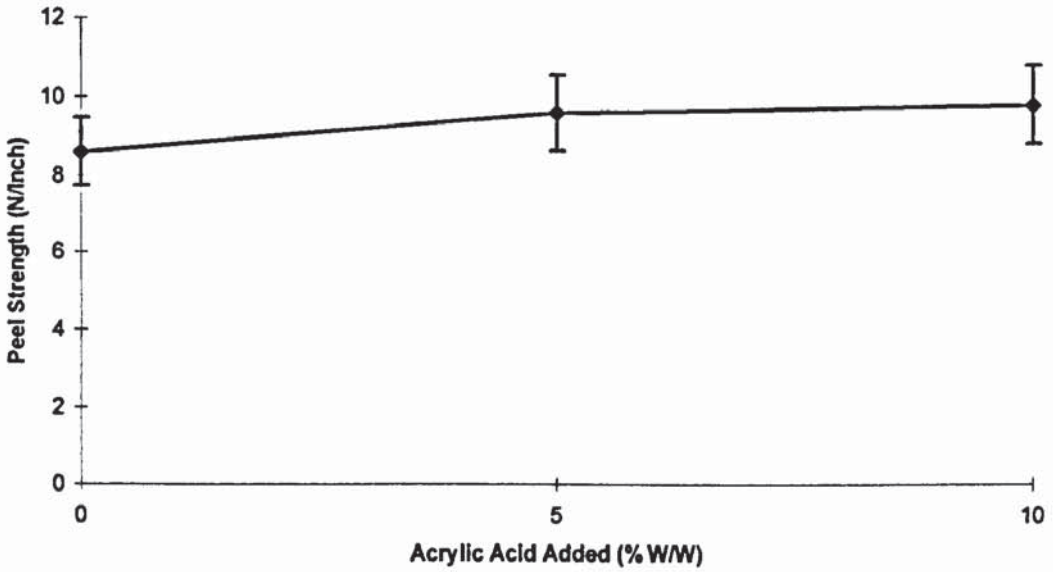


Figure 6.20 Peel Strength of a NaAMPS gel (40% NaAMPS, 28% glycerol and 32% water) with 8.2% DM 137 hydrogel with increasing percentage of acrylic acid.

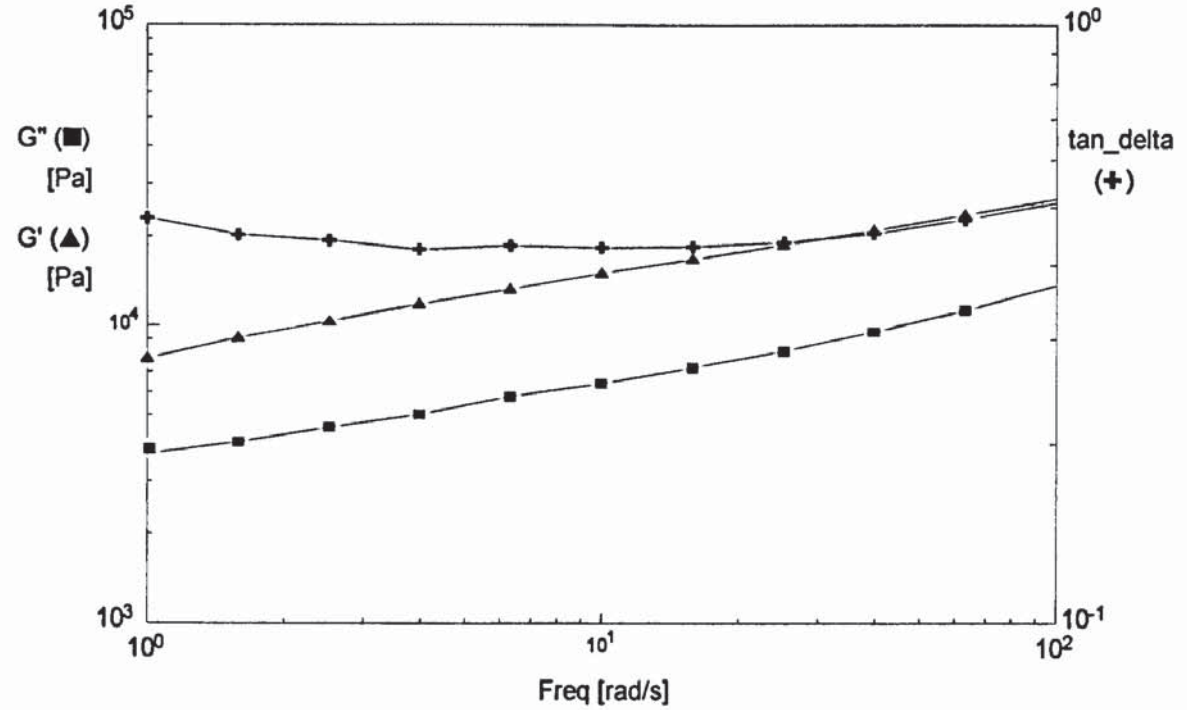


Figure 6.21 The rheological properties of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with 5 % added acrylic acid and 8.2 % DM 137 at 37 °C 1-100 rad/s.

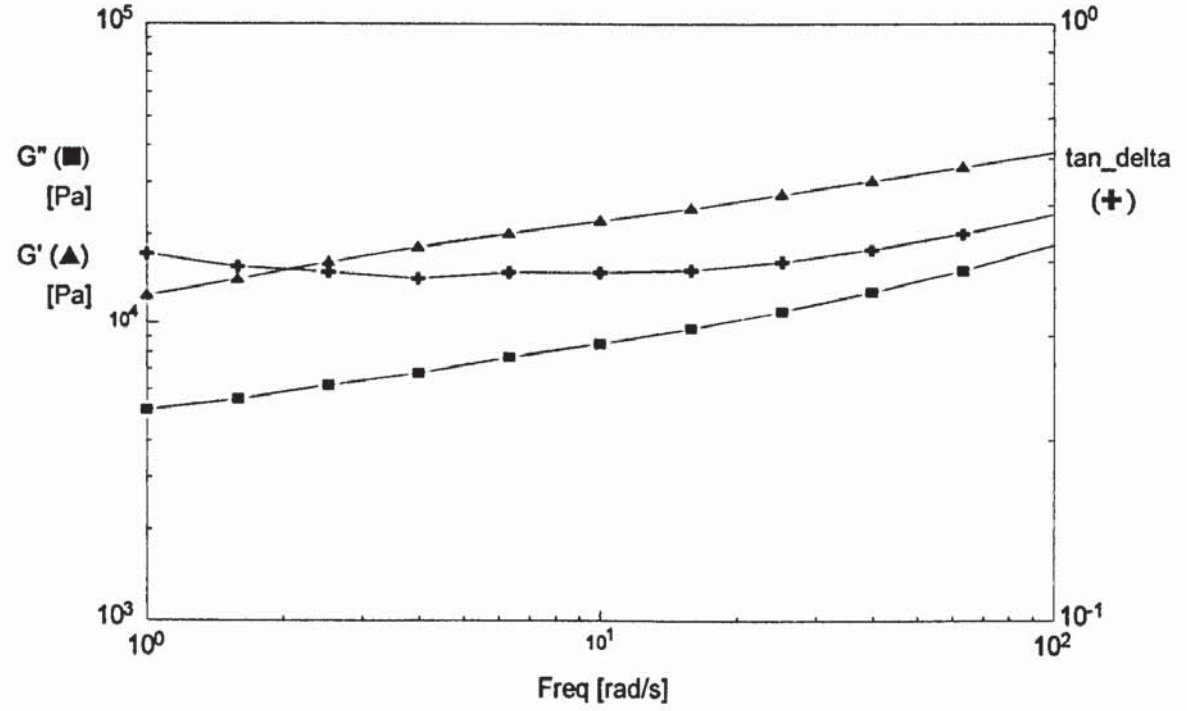


Figure 6.22 The rheological properties of a NaAMPS hydrogel (40% NaAMPS, 28% glycerol and 32% water) with 10 % added acrylic acid and 8.2% DM 137 at 37°C 1-100 rad/s.

6.6.4.2 The Effects of DM 137 and Acrylic Acid

Comparison of the peel strengths showed that the addition of acrylic acid increases peel strength in the presence and absence of DM 137 (fig. 6.20 and 6.10 respectively) as does the addition of DM 137 in the presence and absence of acrylic acid (fig. 6.20 and 6.16 respectively). The effects are complementary and this was due to the acrylic acid and DM 137 acting at different sites, the acrylic acid acting within the gel and DM 137 on the surface of the gel.

The addition of acrylic acid to a DM 137 gel caused the polar component of the gel to increase slightly and the dispersive component to remain high, which resulted in an increase in surface free energy. The high dispersive component was caused by the DM 137 finding its way to the surface of the gel which increased peel strength by interacting with the skin lipids. The acrylic acid increased peel strength by removing residue from the surface of the gel and acted within the gel shown by a minimal effect on the surface free energy of the gel when high percentages of acrylic acid were added to the system (fig. 6.9).

The cohesive strength of the gel increased with an increased addition of acrylic acid to the NaAMPS hydrogel (fig 6.11, 6.12, 6.13) and increased with the addition of DM 137 (fig. 6.16 and 6.17). Addition of both acrylic acid and DM 137 increased the cohesive strength further than either components alone (fig. 6.19 and 6.20), which again suggested that the acrylic acid and DM 137 acted at different sites. The acrylic acid had the greatest effect on cohesion due to the inter molecular interactions. The acrylic acid increased the inter molecular bonding which affected the energy barrier to rotation. The acrylic acid increased the water binding properties of the gel which holds the molecule apart allowing the increased mobility of chains within the gel which in turn enabled increased inter molecular bonding of the amide group with the sulphonate group of NaAMPS.

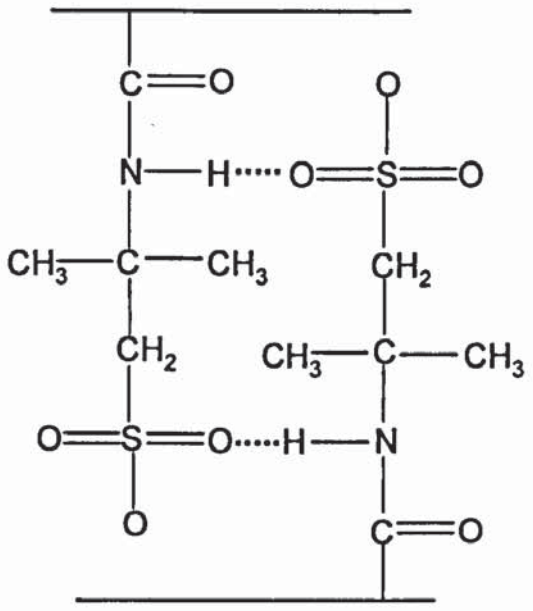


Figure 6.23 The intermolecular interactions between the amide group and the sulphonate group of a NaAMPS gel (40% NaAMPS, 28% glycerol and 32% water).

6.7 Gel Quality and Adhesion Optimisation

The effects of adding acrylic acid, DM 137 and both DM 137 with acrylic acid, was determined for gels containing 70% NaAMPS and 30% SPA as combined ionic monomer. This enabled a comparison to be made between NaAMPS alone and NaAMPS with SPA, to identify any substantial variation in the properties, in particular adhesion and cohesion. The formulations of the three series of gels tested are shown below in tables 6.9, 6.10 and 6.11.

6.7.1 The Effects of Acrylic Acid on SPA Gels

Acrylic acid has been found to increase intermolecular interaction and to decrease the amount of residue detected in NaAMPS-based gels. The acrylic acid was added to the mixed NaAMPS-SPA gels in increments of two percent and the formulae tested are shown below.

NaAMPS (%)	SPA (%)	Glycerol (%)	Water (%)	Acrylic Acid (% added)	PI/XL (%)
28	12	28	32	2	0.1
28	12	28	32	4	0.1
28	12	28	32	6	0.1
28	12	28	32	8	0.1
28	12	28	32	10	0.1

Table 6.9 Compositions (w/w) of gels with increased amounts of acrylic acid used to investigate the effect on cohesion and adhesion.

6.7.1.1 The Addition of Acrylic Acid to a 7:3 NaAMPS:SPA Hydrogel on Surface Free Energy and Peel Strength

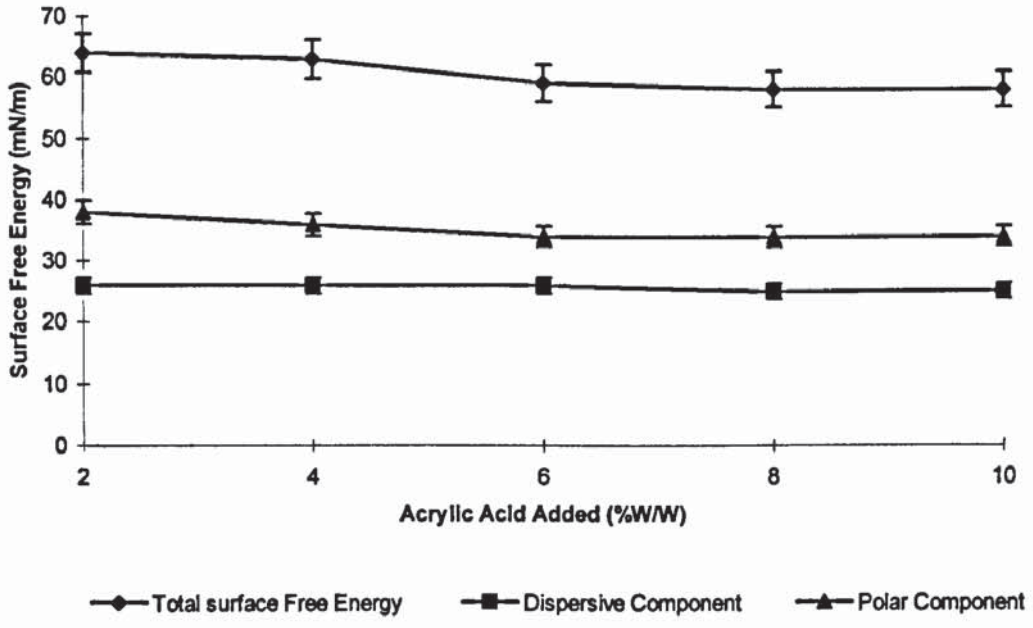


Figure 6.24 The surface free energy of a 7:3 NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%), with increasing percentage of added acrylic acid.

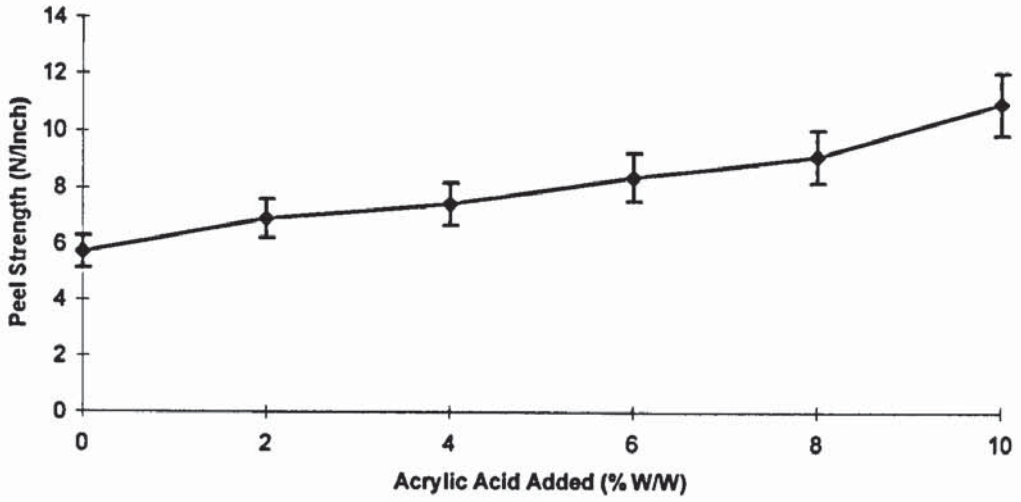


Figure 6.25 The peel strength of a 7:3 NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with increasing percentage of acrylic acid.

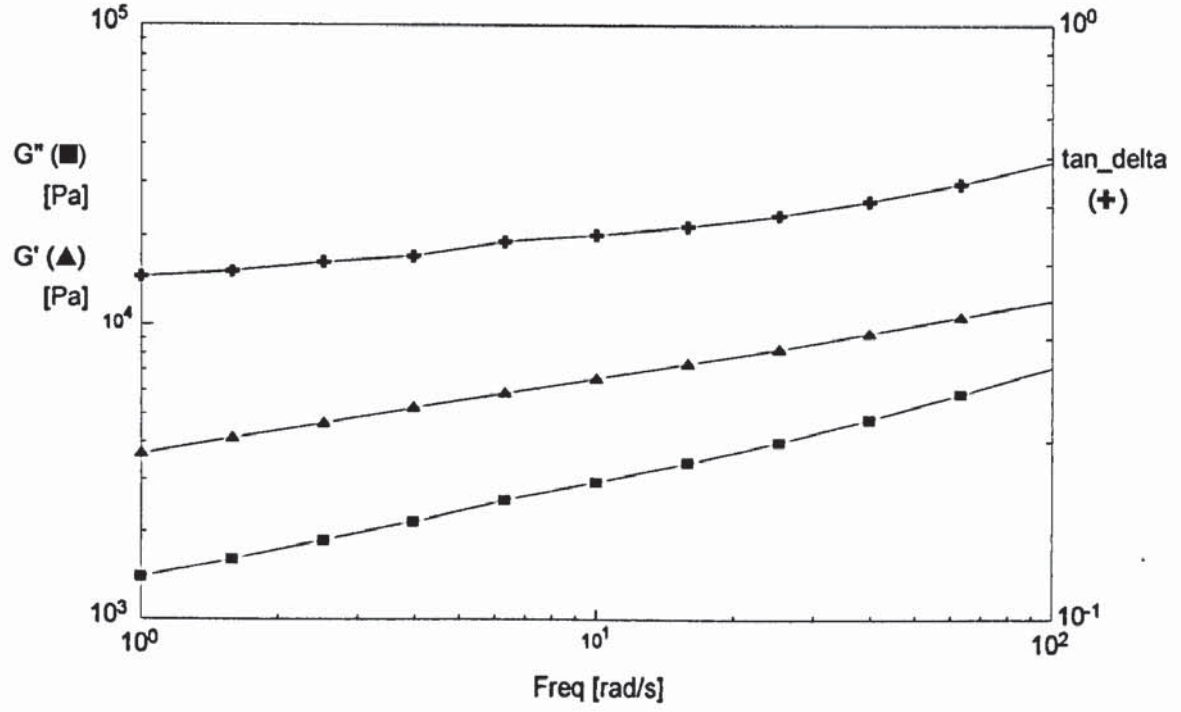


Figure 6.26 The rheological properties of a NaAMPS:SPA hydrogel (28% NaAMPS, 12% SPA, 28% glycerol and 32% water) at 37 °C 1-100 rad/s.

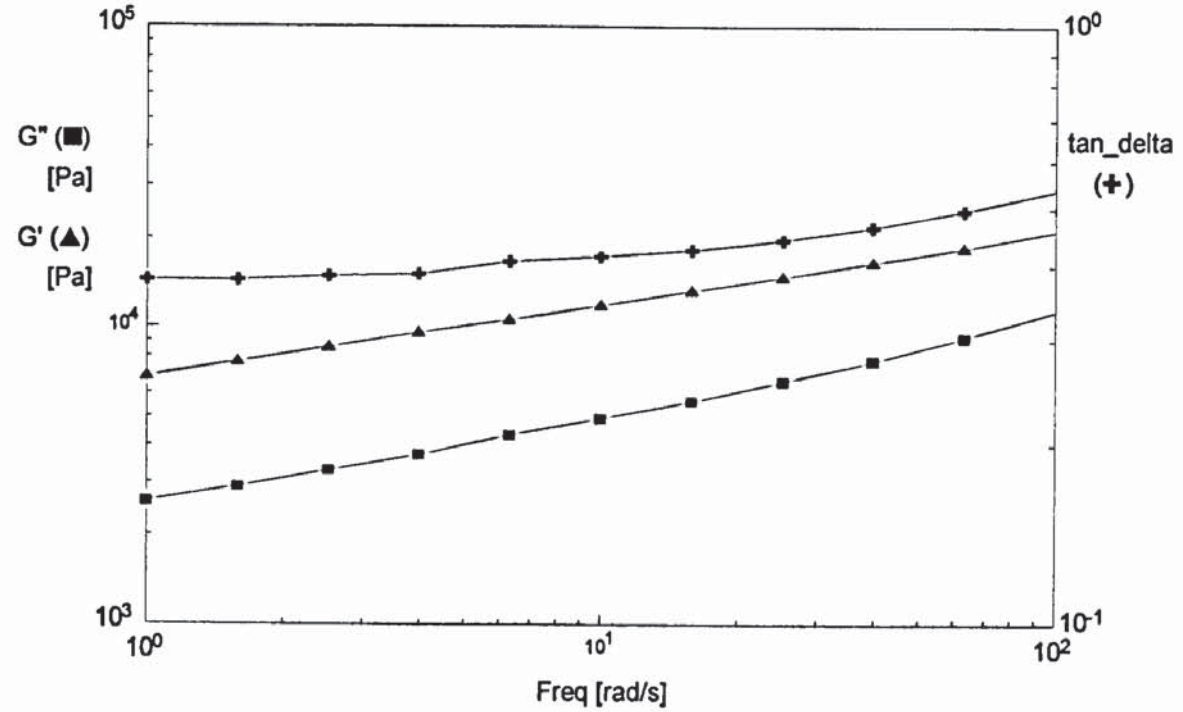


Figure 6.27 The rheological properties of a NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with 5 % added acrylic acid at 37°C 1-100 rad/s.

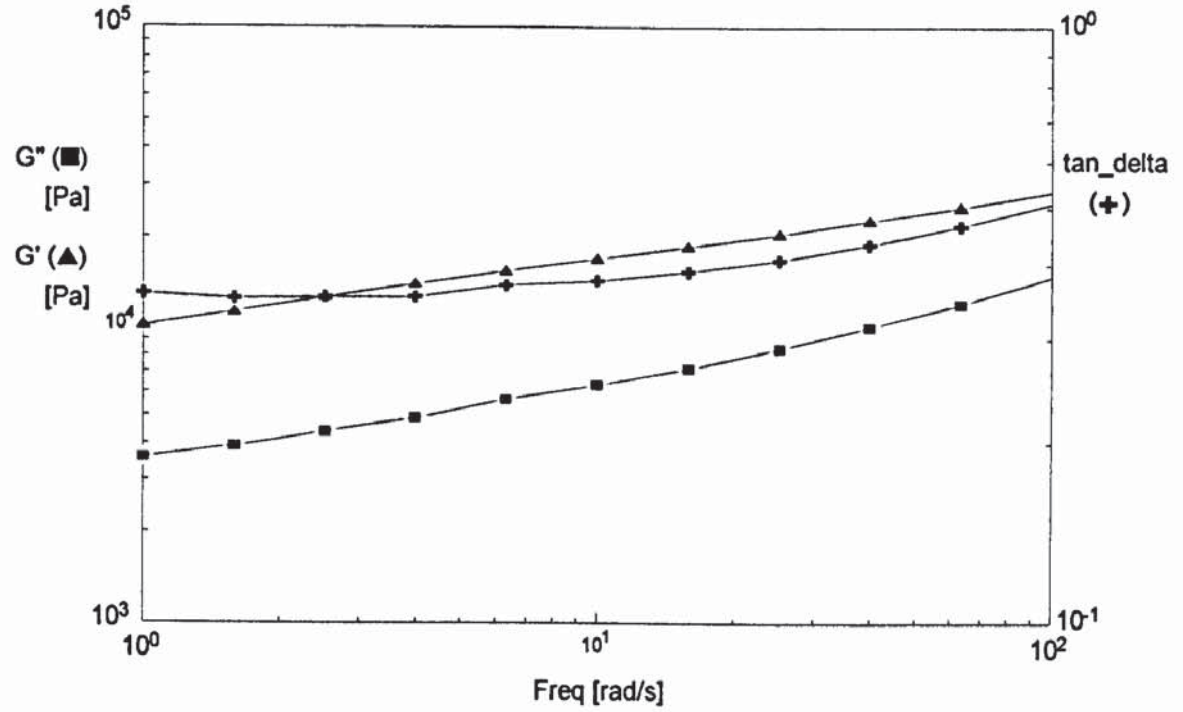


Figure 6.28 The rheological properties of a NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with 10 % added acrylic acid at 37 °C 1-100 rad/s.

6.7.1.2 The Effects of Acrylic acid on Surface Free Energy, Adhesion and Dynamic Mechanical Properties

As with NaAMPS hydrogels, the addition of acrylic acid to the system greatly reduces the amount of residue. It can be seen that the peel strength increases as the percent of acrylic acid increases (figure 6.25), this could be due to the hydrogen bonding groups of acrylic acid. The acrylic acid is very polar and hydrophilic, causing water to be strongly attracted to it, pulling the aqueous layer from the surface. The increased hydrophilic potential and lack of surface residue enables the gel to be more adhesive.

Again, as with NaAMPS alone, the polar component of the gel increases slightly causing the total surface free energy to increase slightly. The increase in the polar component due to the addition of acrylic acid is marginal as the water is being held tight within the gel by the hydrogen bonding, removing some of the polar component from the surface of the gel.

As with NaAMPS the gels studied followed a similar trend, that is, that at a frequency of 1 rad/s there was a low G' and low G'' which increased as the frequency increased and tan delta only increased slightly with increasing frequency. This demonstrates that the viscoelastic properties increase with frequency.

The addition of acrylic acid causes an increase in G' and G''(figure 6.27 and 6,28) compared to the NaAMPS:SPA hydrogels alone (figure 6.26) as with NaAMPS hydrogels, indicating that addition of acrylic acid to the gel causes an increase in the cohesive strength of the adhesive. Again, this may be a result of hydrogen bonding.

6.7.2 The Addition of Emulsified Poly (ethylene-co-vinyl acetate), (DM 137)

DM 137 is 50% polymer, poly(ethylene-co-vinyl acetate), suspended in solution to form an emulsion. The addition of DM 137 is expected to increase the hydrophobic forces on the surface of the gel and it is thought this may enhance adhesion. The components used to produce gels containing DM 137 are shown below.

NaAMPS (%)	SPA (%)	Glycerol (%)	Water (%)	DM 137 (% added)	PI/XL (%)
28	12	28	32	0	0.1
28	12	28	32	4.1	0.1
28	12	28	32	8.2	0.1

Table 6.10 Compositions (w/w) of gels used to investigate the increasing percentage of DM 137.

6.7.2.1 The Effect of the Addition of Poly (ethylene-co vinyl acetate) to a 7:3 NaAMPS:SPA Hydrogel on Surface Free Energy and Peel Strength

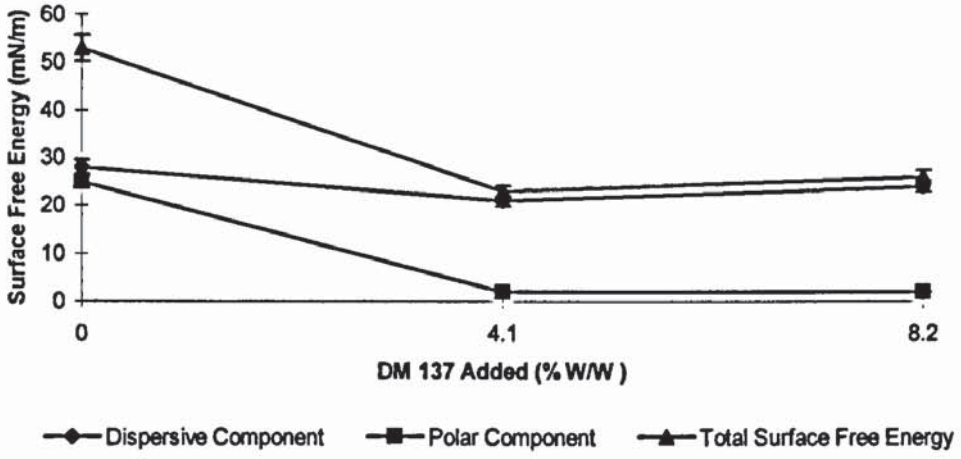


Figure 6.29 The surface free energy of a 7:3 NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with increasing percentage of DM137.

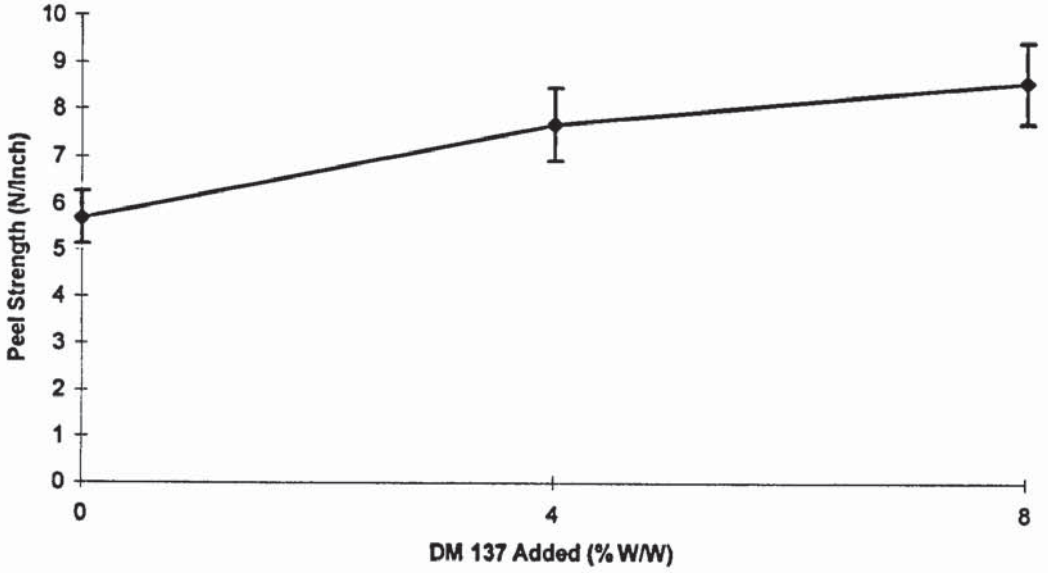


Figure 6.30 The peel strength of a 7:3 NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with increasing percentage of DM 137.

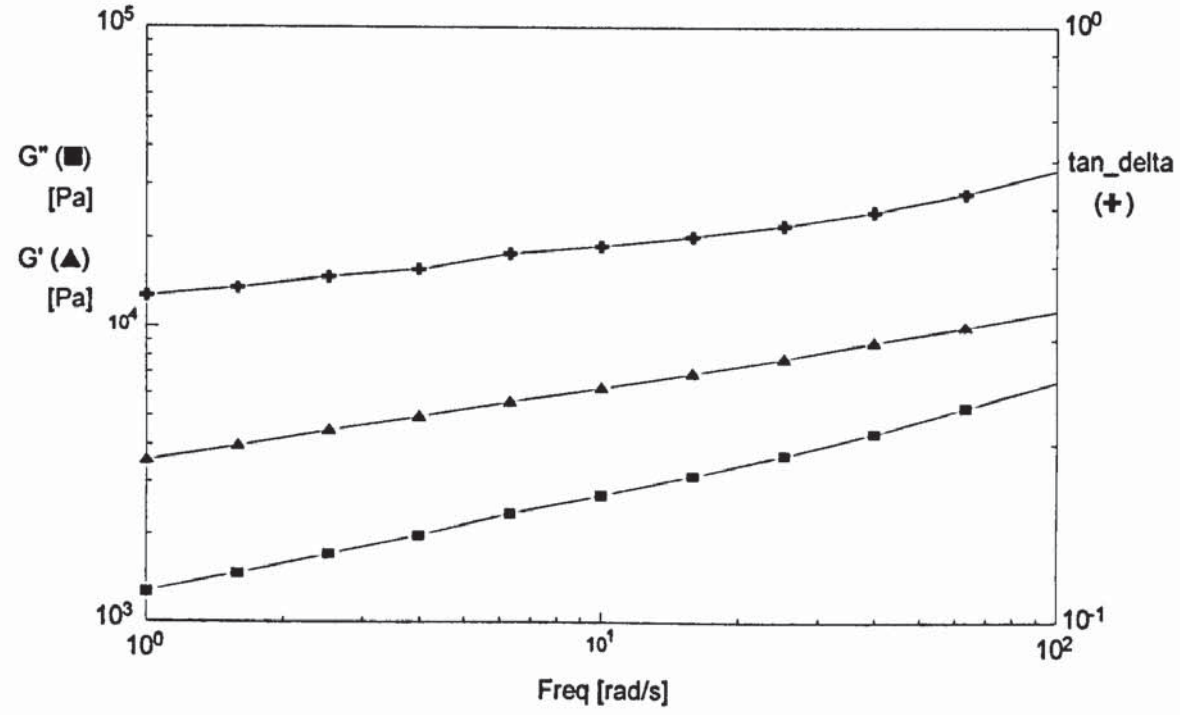


Figure 6.31 The rheological properties of a NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with 5 % added DM 137 at 37°C 1-100 rad/s.

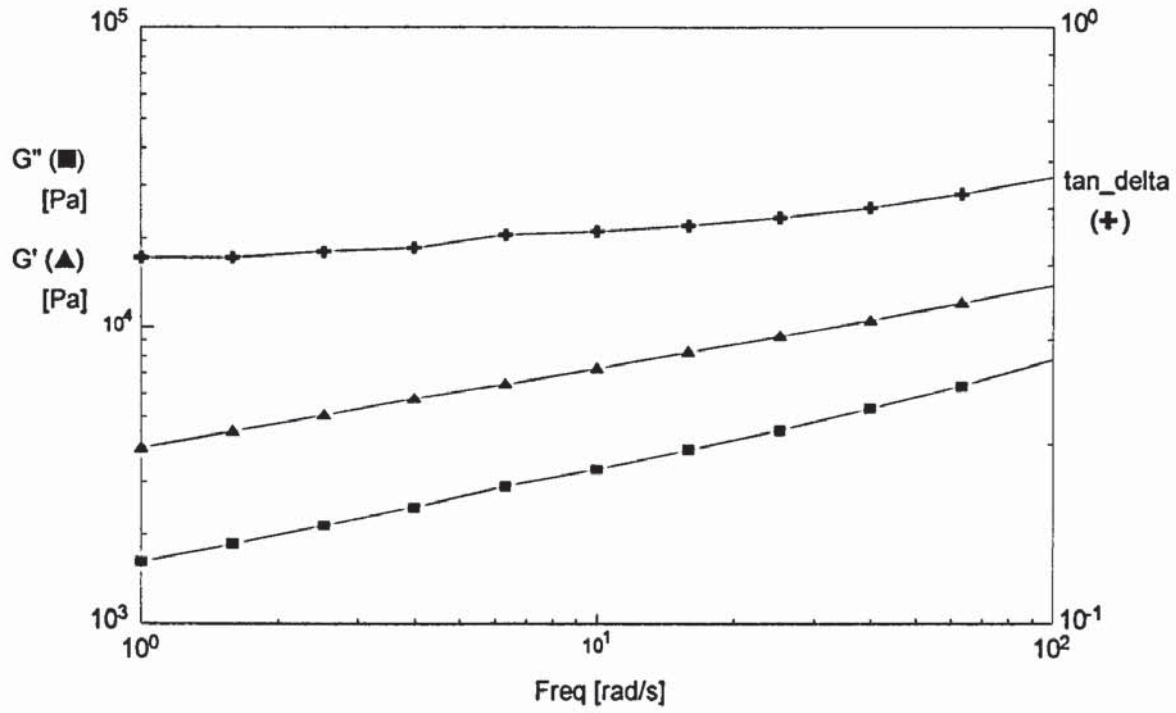


Figure 6.32 The rheological properties of a NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with 10 % added DM 137at 37 °C 1-100 rad/s.

6.7.2.2 The Effects of DM 137 on Surface Free Energy and Adhesion

As with NaAMPS hydrogels, the addition of DM 137 increased the adhesive properties of the gels. The addition of DM 137 caused the polar component of the gel to decrease so that the ratio of dispersive to polar component increases, giving a decrease in surface free energy (figure 6.29). The increase in the ratio of dispersive to polar component and the lower surface free energy enhances adhesion to the hydrophobic lipids of the skin. For an adhesive to adhere to an adherend, the measured surface energy of the gel must be equal to or less than the adherend. The decrease in total surface free energy could be contributing to the peel strength.

The dynamic mechanical properties of the NaAMPS:SPA skin adhesives containing DM 137 (figure 6.31 and 6.32) showed that the DM 137 is not having a significant effect on

cohesive strength of the gel compared to NaAMPS:SPA alone (figure 6.26). Which is to be expected as DM 137 acts on the surface of the gel.

6.7.3 Addition of Acrylic Acid to a 7:3 NaAMPS:SPA Gel with 8.2% DM 137

The larger amount of DM 137 was added to the series of gels containing NaAMPS:SPA because from previous experiments it was found to give a good peel strength and is believed to interact with the skin lipids. As mentioned previously, 8.2% is the highest percentage that can be added because at greater values DM137 is no longer evenly dispersed, and fails to produce homogeneous solution.

Acrylic acid was added because it was known from earlier experiments to increase peel strength and reduce residue on the surface of the gel by increasing hydrogen bonding. The previous results showed that as the percentage of acrylic acid added increased so to did adhesion and consequently both a mid and high percentage of acrylic acid were selected for incorporation.

NaAMPS (%)	SPA (%)	Glycerol (%)	Water (%)	Acrylic Acid (% added)	DM 137 (% added)	PI/XL (%)
28	12	28	32	0	8.2	0.1
28	12	28	32	5	8.2	0.1
28	12	28	32	10	8.2	0.1

Table 6.11 Compositions (w/w) of gels used to investigate the increasing percentage of acrylic acid.

6.7.3.1 The Addition of Acrylic Acid to a 7:3 NaAMPS:SPA Containing 8.2%DM 137 Hydrogel on Surface Free Energy and Peel Strength

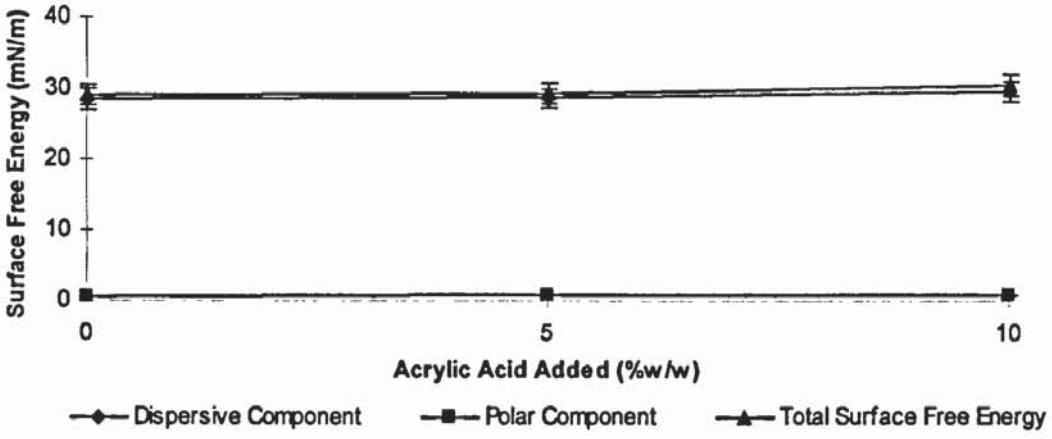


Figure 6.33 The surface free energy 7:3 NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with 8.2% added DM137 and increasing percentage of acrylic acid.

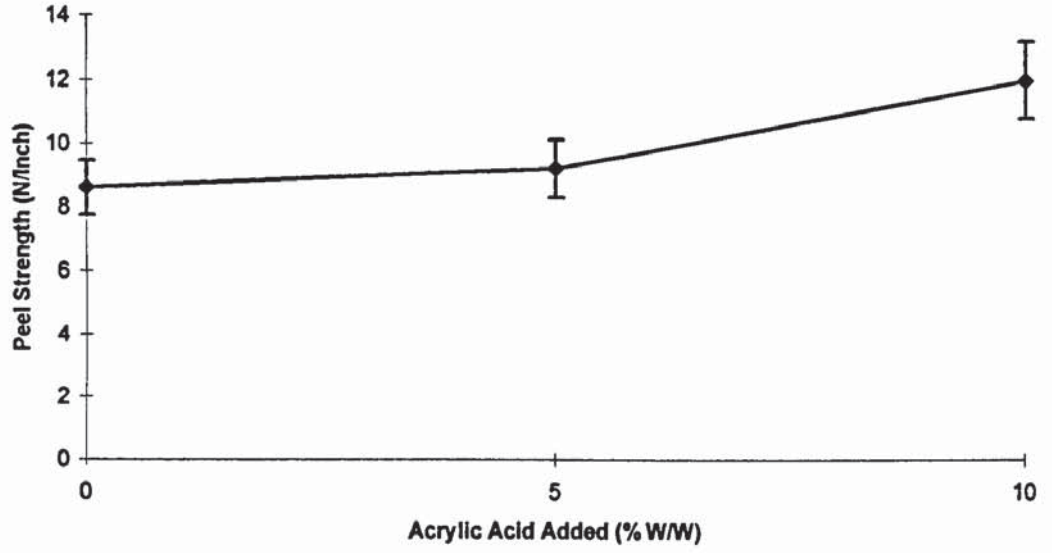


Figure 6.34 The peel strength of a 7:3 NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with 8.2% added DM137 and increasing percentage of acrylic acid.

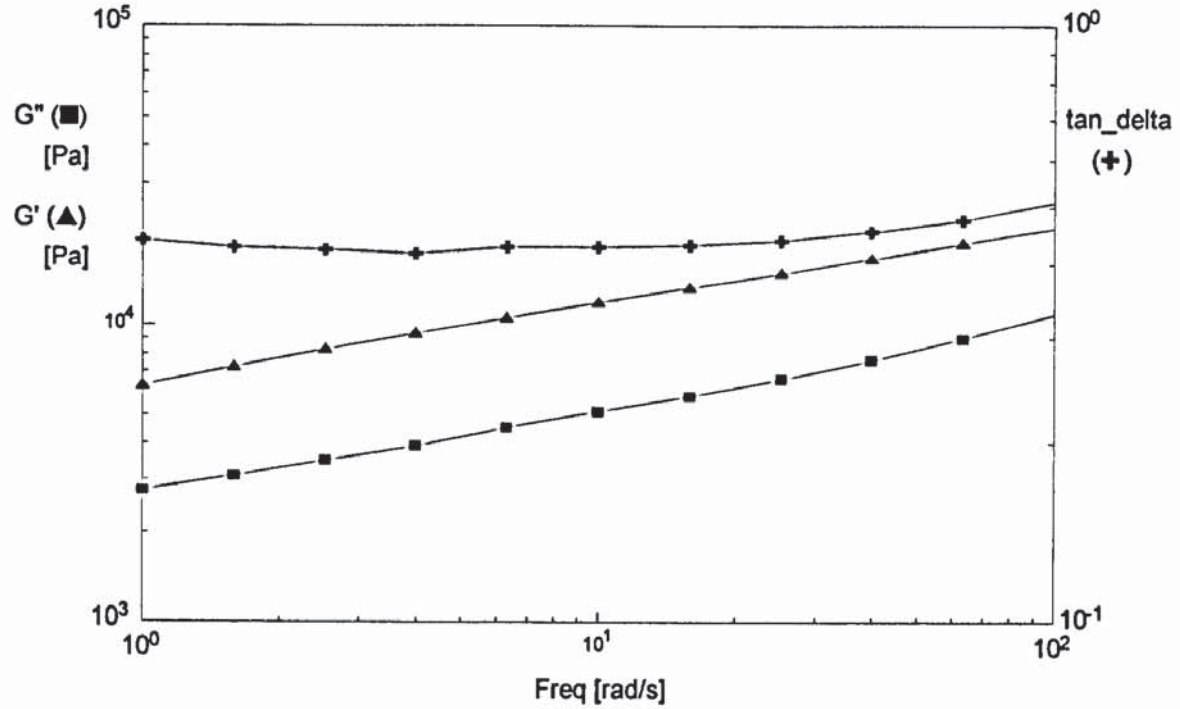


Figure 6.35 The rheological properties of a NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with 5 % added acrylic acid and 8.2% DM 137at 37°C 1-100 rad/s.

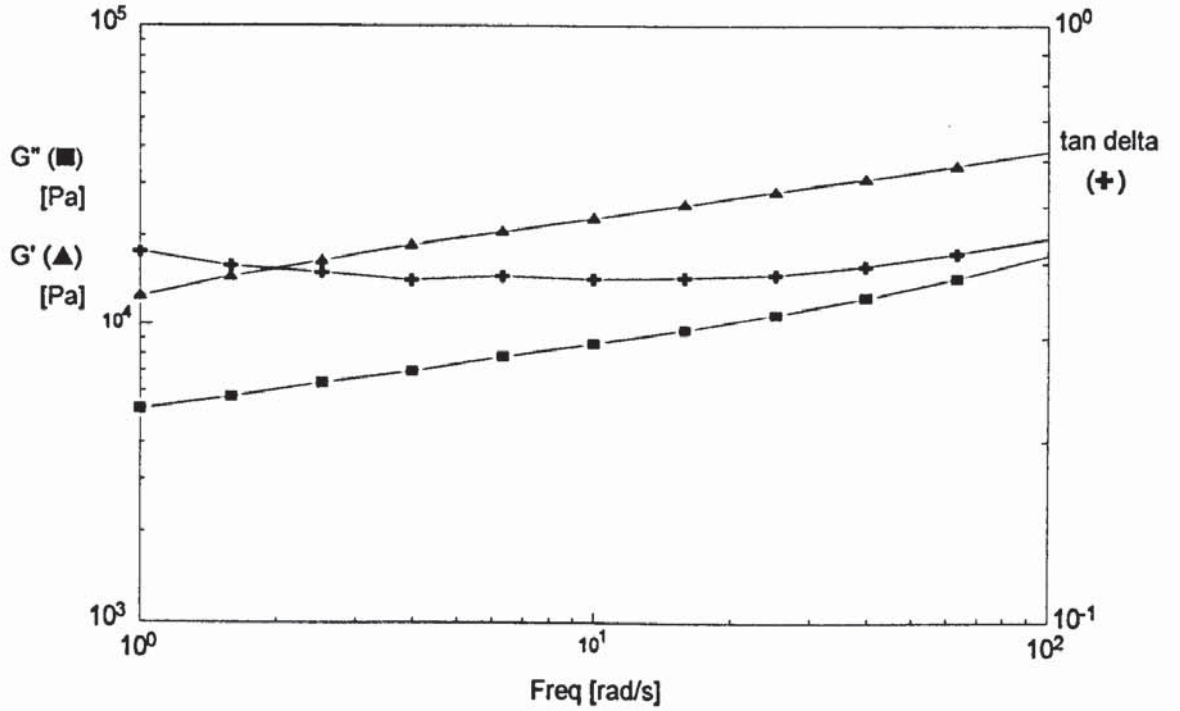


Figure 6.36 The rheological properties of a NaAMPS:SPA hydrogel (NaAMPS 28%, SPA 12%, glycerol 28 % and water 32%) with 10 % added acrylic acid and 8.2% DM 137at 37°C 1-100 rad/s.

6.7.3.2 The Effects of Acrylic Acid and DM 137 on Surface Free Energy and Adhesion

The combination of DM 137 and acrylic acid gave gels with better adhesion than either component used alone. This is because of the reduced residue due to the acrylic acid and the hydrophobic interaction of DM 137 with the skin lipids. 5% added acrylic acid was found to be adequate to bring about this effect as is shown in figure 6.34. The polar component appears to have been masked by the dispersive component due to the predominant effect of DM 137.

As before the dynamic mechanical properties increased with increasing frequency of rad/s. Adding acrylic acid increased the cohesive strength as before, with the highest percentage of acrylic acid increasing the cohesive strength the greatest.

6.7.4 Comparison of NaAMPS and NaAMPS:SPA hydrogels

These gels followed the same trend as the NaAMPS gels, supporting the validity of the previous experiments. However differences occur where G', G'' and tan δ cross the axis, (compare figures 6.11-13 with 6.26-28, 6.17-18 with 6.30-31 and 6.31-32 with 6.35-36). The values of G', G'' and tan delta are higher for NaAMPS gels, suggesting that the addition of SPA to the system lowers the cohesive strength of the gels. This is supported by the fact that NaAMPS:SPA gels did not fully return to their original shape after peel testing whereas the NaAMPS gels did and moreover, the NaAMPS gels felt tougher and were easier to work with than the NaAMPS:SPA gels.

6.8 Kinetic Contact Angle analysis of NaAMPS and SPA Hydrogels on the GBX Goniometer

Kinetic analysis was performed on a series of NaAMPS gels and an SPA gel to determine the absorption properties of the gel over a short period of time. SPA was used without NaAMPS to highlight any differences between the ionic monomers because the difference between a 7:3 NaAMPS:SPA hydrogel and NaAMPS will be magnified.

The surface of the adhesive hydrogels were examined with drops of diiodomethane and water over a period of time to determine the properties of the materials. Water is expected to be absorbed into the gel as the hydrophilic gels have a high affinity for water. Diiodomethane is not expected to interact with the hydrogel as much. The formulations tested are shown below:

SPA (%)	NaAMPS (%)	Glycerol (%)	Water (%)	Acrylic Acid (% added)	DM 137 (% added)	PI/XL (%)	Figure
40	0	28	32	0	0	0.1	6.37
0	40	28	32	0	0	0.1	6.38
0	40	28	32	10	0	0.1	6.39
0	40	28	32	0	8.2	0.1	6.40

Table 6.12 Compositions (w/w) of gels used for the kinetic analysis of NaAMPS gels and an SPA gel

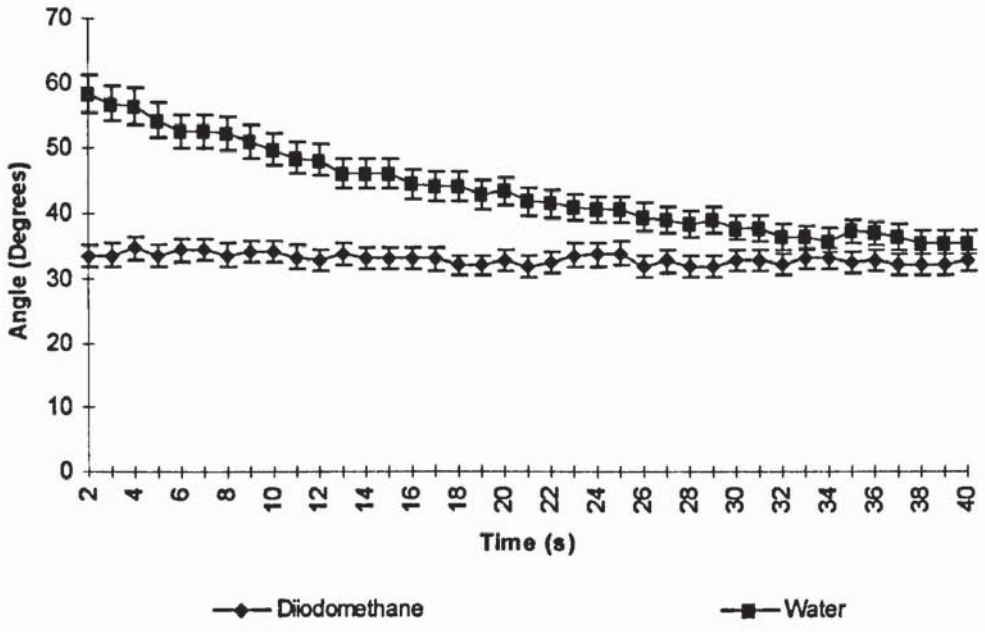


Figure 6.37 The graph demonstrates the contact angles against time, obtained from diiodomethane and water on an SPA hydrogel.

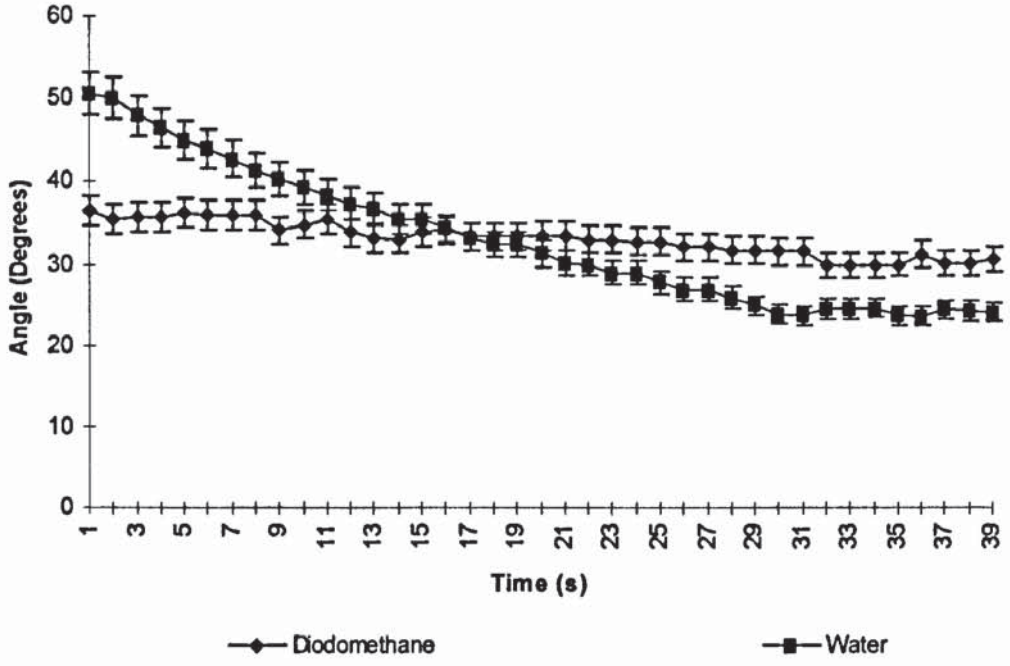


Figure 6.38 The graph demonstrates the contact angles against time, obtained from diiodomethane and water on an NaAMPS hydrogel.

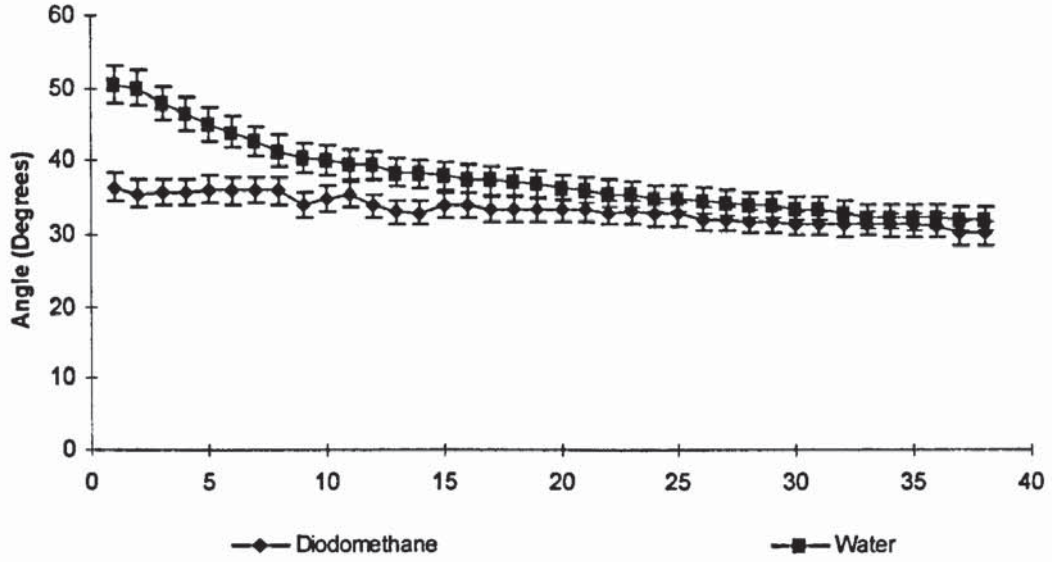


Figure 6.39 The graph demonstrates the contact angles against time, obtained from diiodomethane and water on a NaAMPS and 10% acrylic acid hydrogel.

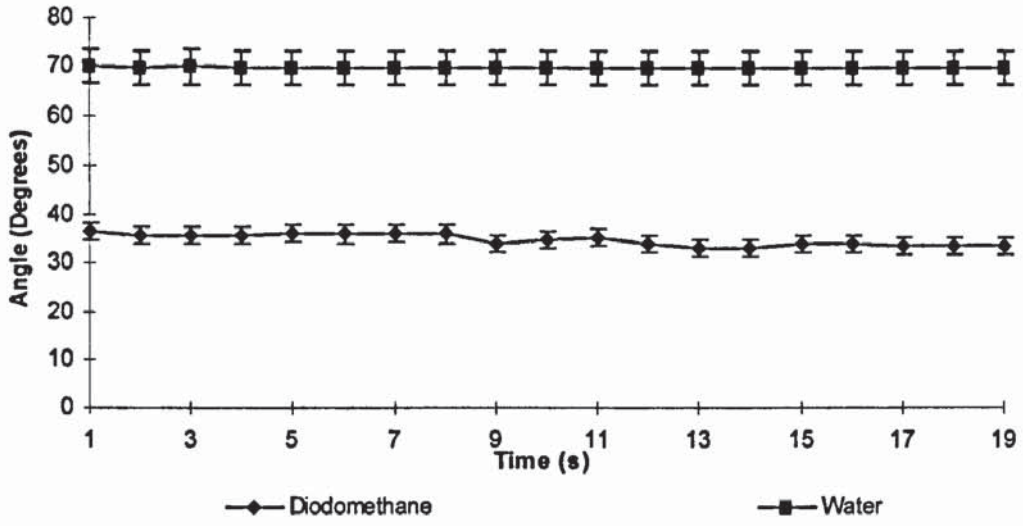


Figure 6.40 The graph demonstrates the contact angles against time, obtained from diiodomethane and water on an NaAMPS and 8.2% DM137 hydrogel.

6.8.1 Comparison of the SPA and NaAMPS Hydrogels

Comparison of the hydrogels produced from SPA and NaAMPS (figure 6.37 and 6.38 respectively) showed that both gels showed similar surface properties, they are extremely hydrophilic with a large demand for water. Therefore, they readily absorb water, NaAMPS more so than SPA, hence the lower initial contact angle. Diodomethane, a more hydrophobic liquid was not absorbed readily into the gels as shown by the unchanging contact angles recorded.

The NaAMPS gel containing acrylic acid (figure 6.39) is extremely hydrophilic and the contact angle for water is much like that noted for NaAMPS alone. The water can be seen to be absorbed into the gel shown by the decreasing contact angles whereas the diiodomethane remains unabsorbed and the contact angles remain constant. The NaAMPS gel containing DM137 (figure 6.40) showed higher contact angles than the NaAMPS gel because the emulsion is hydrophobic and prevents the interaction of the liquid with the gel. This is shown by the unchanging contact angles.

6.9 The Adhesive Interface

The surface of the adhesive is of prime importance, being the site which is in contact with the skin and is responsible for removing surface lubrication to enable adhesion to occur. The surface free energy demonstrated the effects of adding different reagents but did not appear to be a good prediction of the adhesive properties of the gels, although, it may do so in other systems. The surfaces of the hydrogels were examined under the microscope after being stained using bromopyrogallol red and then subsequently examined at high and low magnification.

NaAMPS (%)	Glycerol (%)	Water (%)	Acrylic Acid (% added)	DM 137 (% added)	PI/XL (%)	Figure(s)
40	28	32	0	0	0.1	6.42
40	28	32	0	10	0.1	6.44
40	28	32	0	10	0.1	6.45

Table 6.13 Compositions (w/w) of gels examined microscopically.

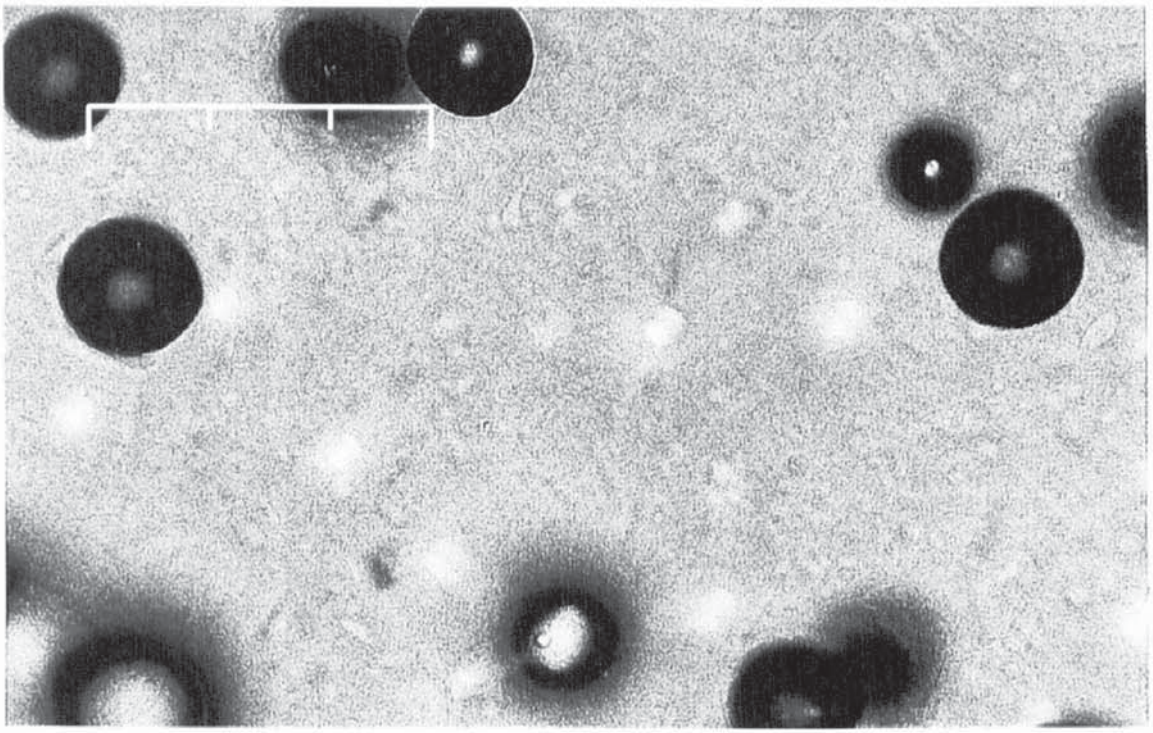


Figure 6.41 The surface of a NaAMPS (NaAMPS 40%, glycerol 28 % and water 32%) skin adhesive stained with bromopyrogallol red at low magnification. Each division represents 0.1mm.

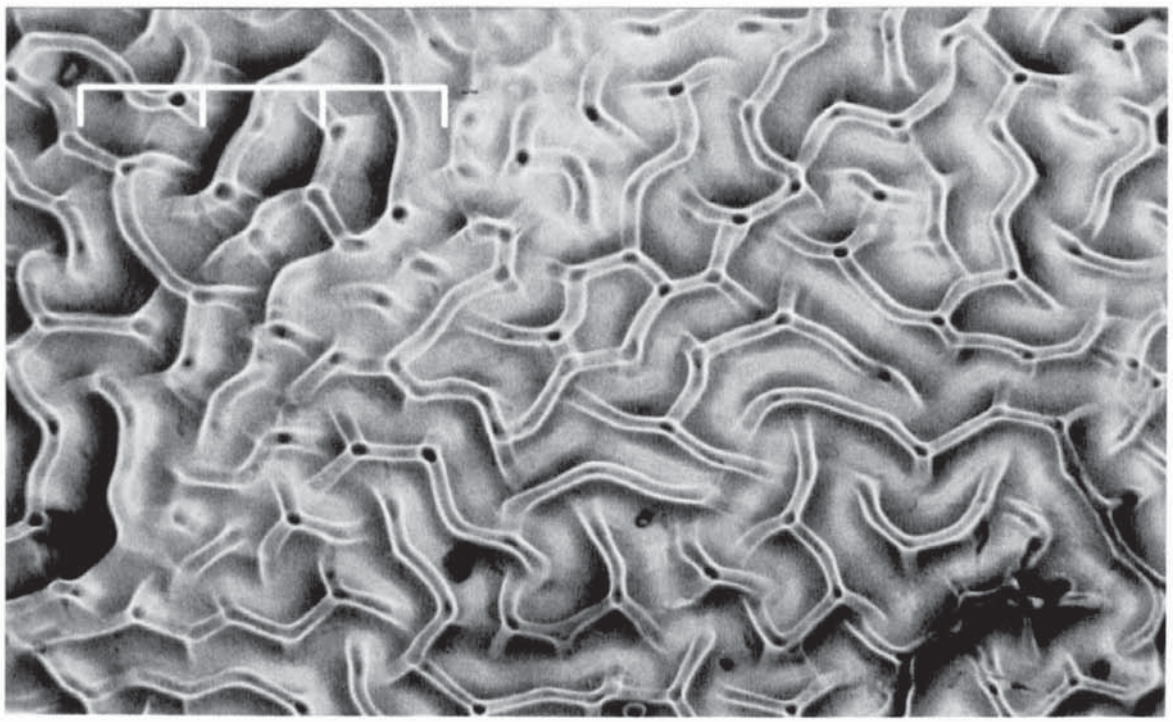


Figure 6.42 The surface of a NaAMPS (NaAMPS 40%,, glycerol 28 % and water 32%) skin adhesive containing 10% DM 137 stained with bromopyrogallol red at low magnification. Each division represents 0.1mm.

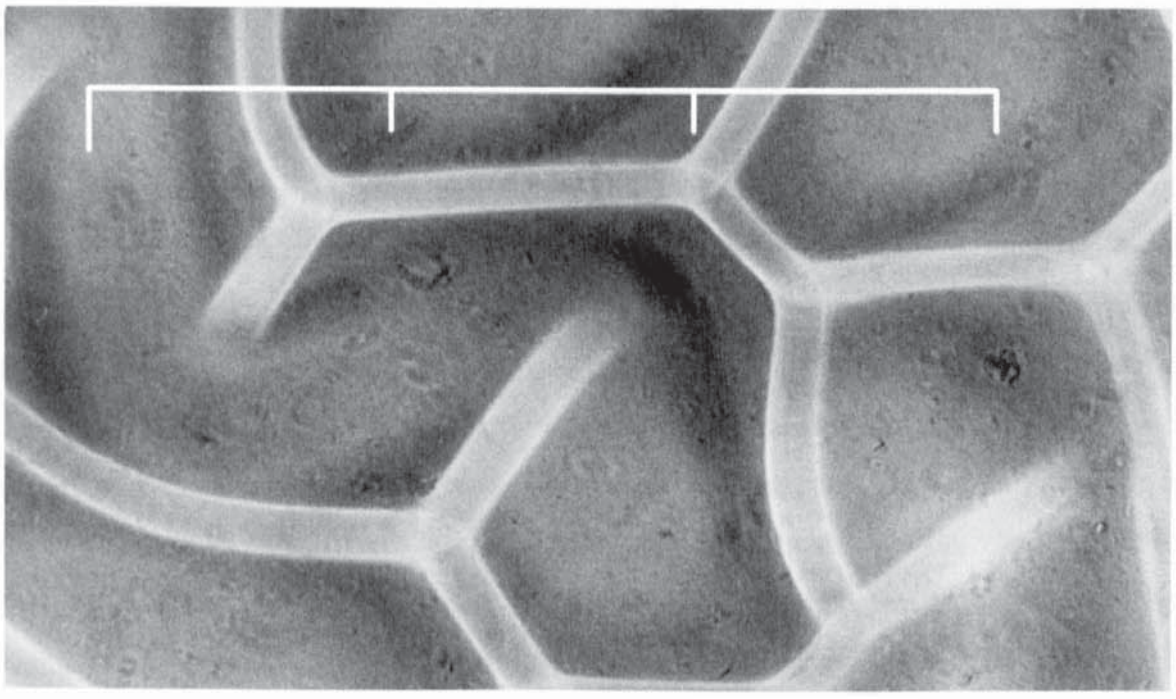


Figure 6.43 The surface of a NaAMPS (NaAMPS 40%, glycerol 28 % and water 32%) skin adhesive containing 10% DM 137 stained with bromopyrogallol red at high magnification. Each division represents 0.1mm.

The surface of the NaAMPS revealed a random non-uniform surface. However, the DM 137 caused the interface to divide into domains. This reinforces the supposition that the DM 137 dominates the surface where the hydrophobic regions separate themselves from the water phase and are presented to the air or hydrophobic skin.

Biphasic polymers can be formed when a hydrophobic and hydrophilic monomer are polymerised in the presence of a reactive solvent bridge e.g. N,N-dimethylacrylamide. As the monomers polymerise the reactive solvent bridge 'disappears' causing the hydrophobic components to separate into a biphasic system.

DM 137 is a hydrophobic polymer emulsion, therefore on polymerisation with the hydrophilic monomer solution a biphasic surface is formed giving hydrophobic and hydrophilic domains.

6.10 Investigation of the Effect of Cure on Water Loss

The water content of a hydrogel is always an important issue as it affects many of its characteristics, including mechanical properties, adhesion and chain rotation. The water content of the gels synthesised were analysed by DSC and it was concluded that for these series of gels, all the water was present in bound form and none was free. Samples of the same gels were weighed, then completely dried in an oven, and re-weighed. Thus, concluding that most of the water in the solution prior to polymerisation, remained in the gel upon completion of curing. To cure gels, the polymer solution is spread thinly over a large surface area, this is subsequently passed under a UV lamp which will also be warm. The large exposed surface area and raised temperature causes some water loss. Some gels require more curing than others and may require being passed under the UV lamp as many as 20 times. Therefore, it is important to know the extent of the water lost from the gel as curing number increases. Additionally, it was important to determine if the water loss was greater for gels with a higher water content and investigate if gels made from less polar monomers may allow evaporation to occur at a faster rate.

Two basic NaAMPS gels were made, one was the standard NaAMPS gel with the same water content to that previously used whilst the other had 5% added water. The gels

were sectioned into samples then weighed and cured for 3, 5, 10, 15, and 20 times and then re-weighed. The total water loss per number of cures was measured as a percentage of the gel weight, for both the normal and high water content gels. The rate of water loss per the number of cures as a percent of the gel weight was also recorded. The results are shown in figure 6.44 and figure 6.45 respectively.

It should be noted that the results show the total water loss which is an average through out the gel. However, the water loss may be different at the exposed surface. It might be expected that the water loss would be greater at the surface, and if this is true, the gel might equilibrate throughout when stored behind a waterproof cover.

6.10.1 Results of Cure on Water Loss

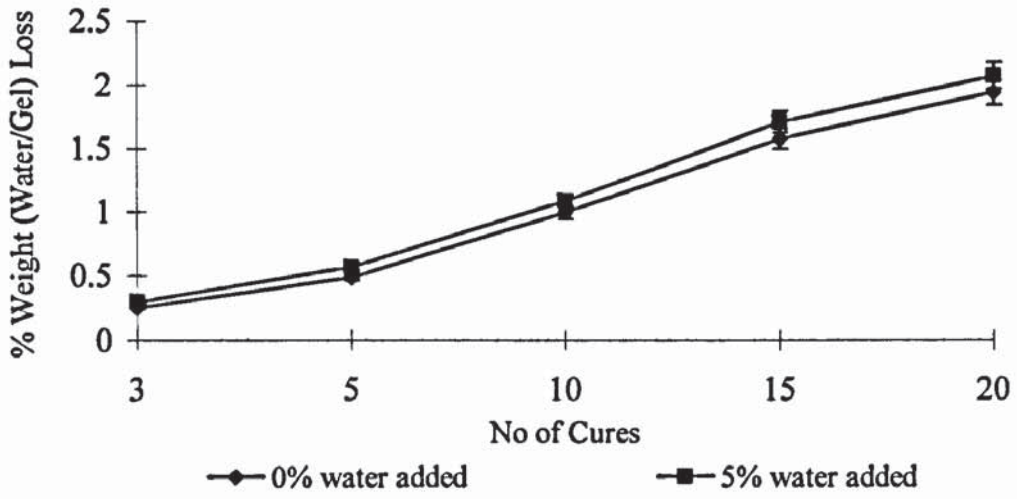


Figure 6.44 The total water loss from 2 NaAMPS gels (NaAMPS 40%, glycerol 28 % and water 32%). One gel contained no additional water to that of the usual formulation and the other contained an additional 5% added water. The water loss per number of cures is measured as a percent of the gel weight.

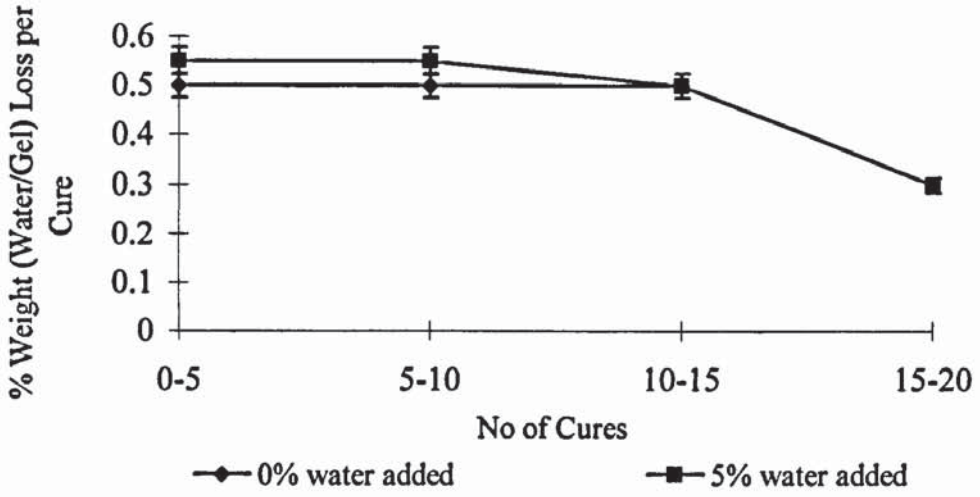


Figure 6.45 The rate of total water loss from 2 NaAMPS gels gels (NaAMPS 40%, glycerol 28 % and water 32%). One gel contains no added water compared to the usual formulation and the other contains 5% added water. The rate of water loss per the number of cures is measured as a percent of the gel weight.

6.10.1.2 The effect of cure on water loss

The total water loss from the gel containing no added water and that containing 5% added water follows the same trend, increased water loss with increasing number of cures. The percent total water loss is slightly higher from the gel containing 5% added water. If we look at the rate of water loss we can see a decrease in the rate of water loss over the number of cures, indicating that most of the water is lost initially. The rate of water loss from the gel with 5% added water is slightly higher at first but levels off after repeated cure cycles.

6.10.2 Dynamic Mechanical Properties of gels after Different Numbers of Passes Under UV Lamp

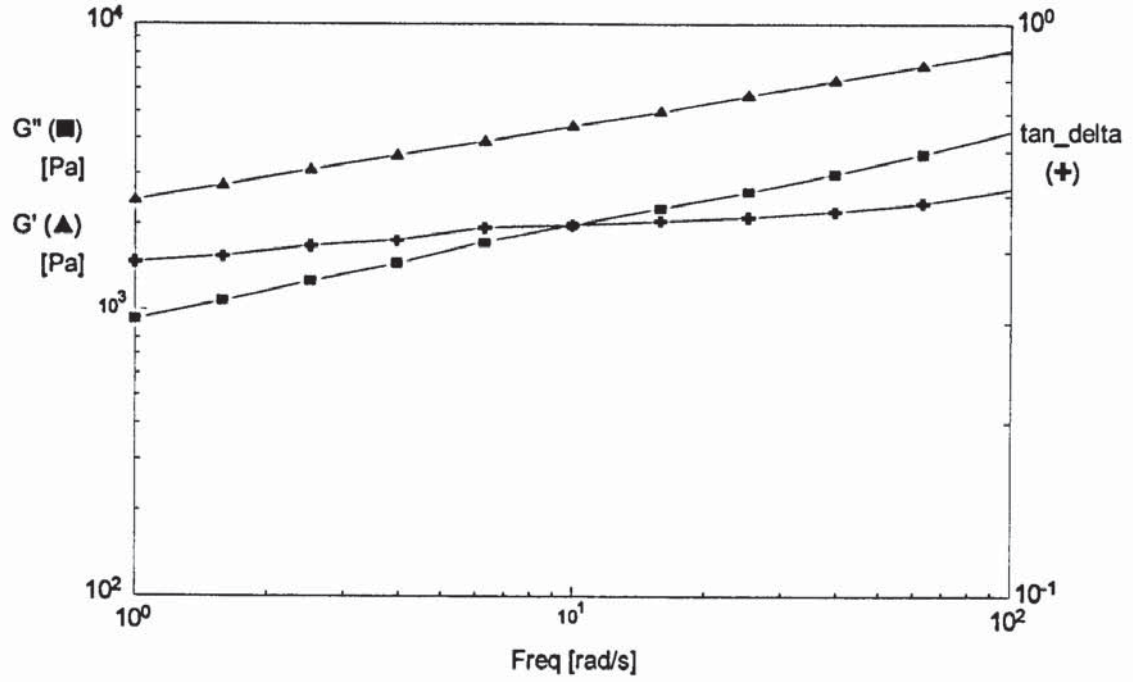


Figure 6.46 The rheological properties of a NaAMPS gel (NaAMPS 40%, glycerol 28 %, water 32%) at 37°C 1-100 rad/s after 5 passes under UV.

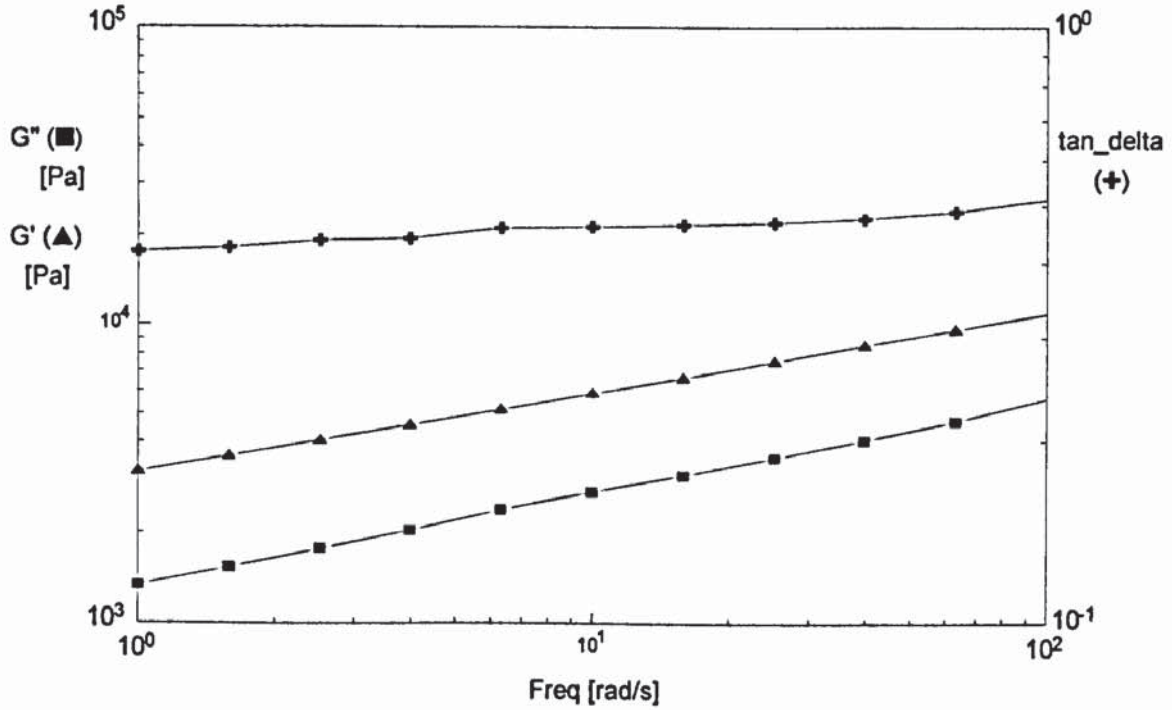


Figure 6.47 The rheological properties of a NaAMPS gel gels (NaAMPS 40%, glycerol 28 % water 32%) at 37°C 1-100rad/s after 10 passes under UV

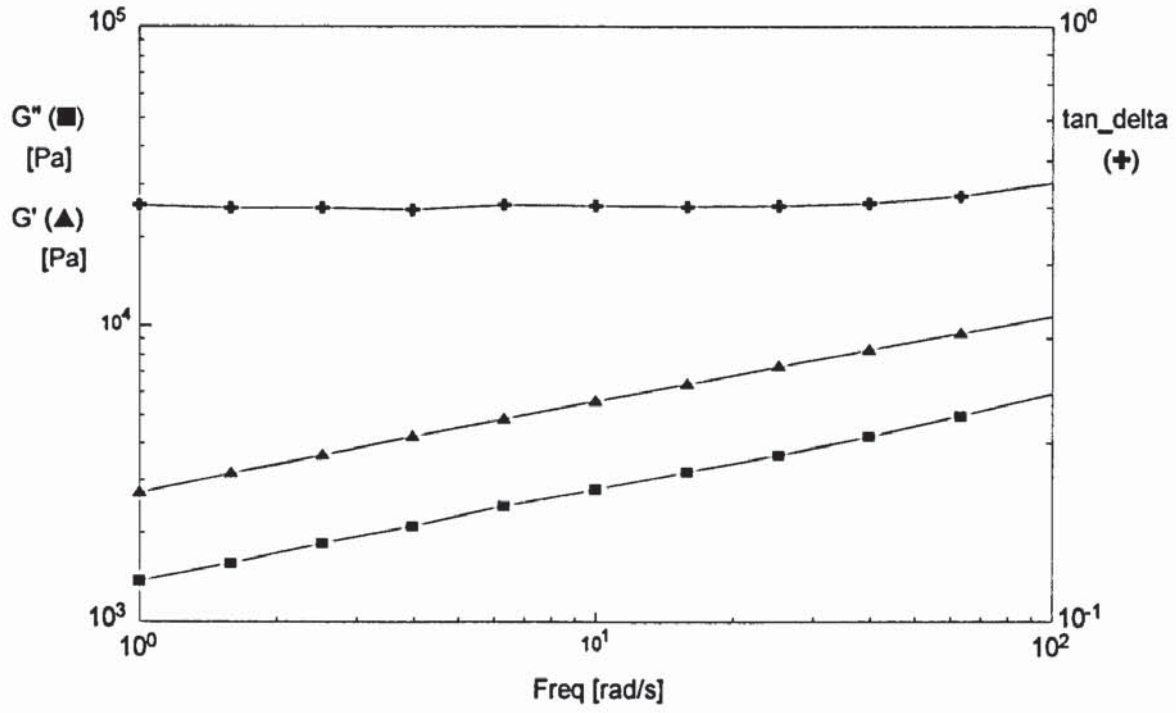


Figure 6.48 The rheological properties of a NaAMPS gel gels (NaAMPS 40%, glycerol 28 % and water 32%) at 37°C 1-100rad/s after 15 passes under UV.

6.10.2.1 Discussion on The Dynamic Mechanical Properties of Gels Experiencing Different Number of Passes Under a UV Lamp

The dynamic mechanical properties of a basic NaAMPS gel was studied to determine the effect of curing on the gels' cohesive strength. If we compare the G' and G'' values of the gel after being passed under the UV lamp five times with a gel that was passed under the UV lamp ten times, we can see that the G', G'' and tan delta values have increased suggesting that the cohesive strength has increased with curing. If we compare the values obtained from a gel that was passed under the UV lamp fifteen times to one passed under the UV lamp ten times we cannot see a significant change in cohesive strength which would indicate that, for NaAMPS gels, there is no need to pass the gels under the UV lamp more than ten times to obtain a well cured gel with good cohesive strength for the monomers used. Additional passes under the UV lamp is too time consuming and of little benefit.

6.10.3 The Surface Free Energy of a NaAMPS Gel after Different Curing Times

The surface free energy of a NaAMPS gel after being passed under the UV lamp for a certain number of passes was analysed. The results are shown below.

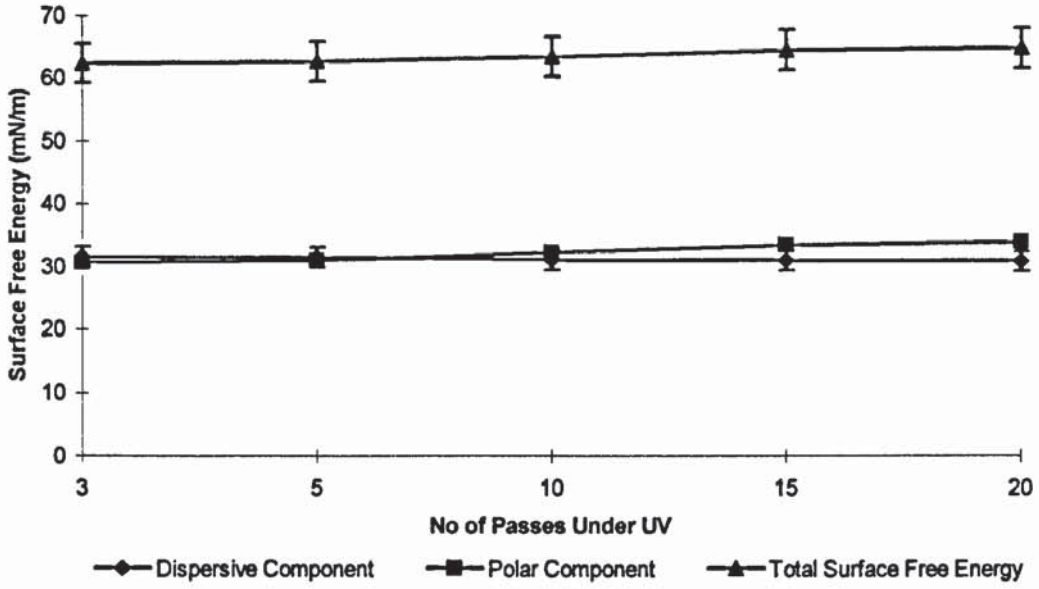


Figure 6.49 The surface free energy of a NaAMPS hydrogel (NaAMPS 40%, glycerol 28 % and water 32%) with increasing passes under UV lamp.

The results show that the surface free energy does not change dramatically. The polar component increases. This may be due to a minimal loss of water as a result of evaporation leading to surface dehydration which, in turn may cause polar groups to rotate towards the surface in an attempt to absorb some moisture.

6.10.4 The Effect of Water Content on Peel Strength

NaAMPS (%)	Glycerol (%)	Water (%)	Water added (%)	PI/XL (%)
40	28	22	0	0.1
40	28	30	8	0.1
40	28	35	13	0.1
40	28	40	18	0.1
40	28	45	23	0.1

Table 6.14 Gel compositions (w/w) used for testing the effects of water content on peel strength.

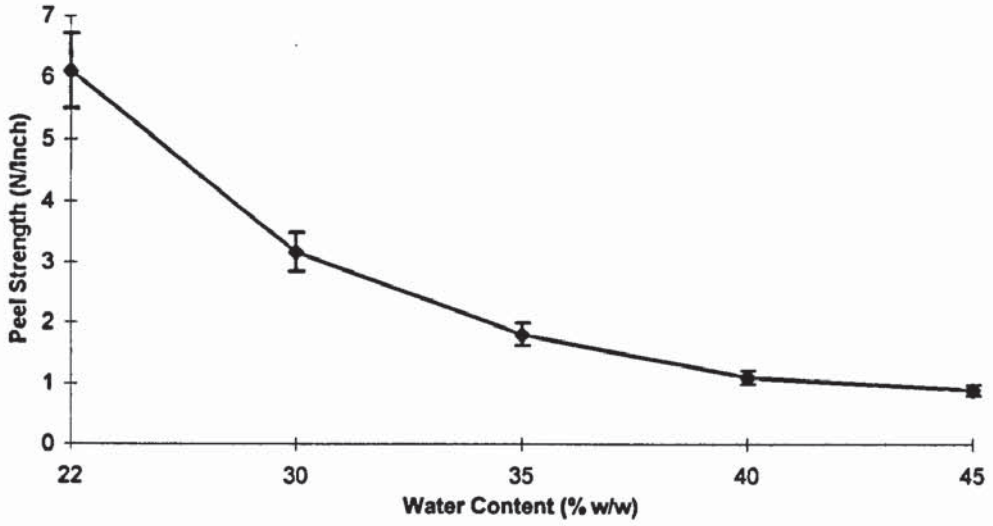


Figure 6.50 The effect of increasing water content on peel strength.

As the water content of the gels increases the peel strength decreases. This could be due to the interfacial layer of water not being removed as efficiently. A further reduction in water content is not possible because this would lead to formation of poor quality gels and, in addition, the NaAMPS would not dissolve. The monomer and glycerol content was kept constant to ensure that the reduction in peel strength did not arise from a reduction in monomer and glycerol present. Although the effect of increasing water content will essentially dilute the concentration of monomer and glycerol.

6.11 Swelling Behaviour

Skin adhesive hydrogels have been produced with good adhesive and rheological properties. However, their function as a skin adhesive may expose them to different environments such as high humidity or even submersion in water. The present skin adhesives would swell to an unacceptable level under these conditions. Therefore, PEG200 Monomethacrylate was added to reduce the swelling of the gels under high moisture conditions without introducing a large number of cross-links such as encountered in the previously investigated PEG dimethacrylate, which provided

extensive cross-linking leading to brittle gels with inferior adhesive properties. The following compositions were tested for swelling and adhesive properties.

NaAMPS (%)	Glycerol (%)	Water (%)	PEG 200 mono-methacrylate (% added)	PI/XL (%)
40	28	32	0	0.1
40	28	32	10	0.1
40	28	32	20	0.1
40	28	32	30	0.1

Table 6.15 Compositions (w/w) of gels used to investigate the increasing percentage of PEG 200 monomethacrylate.

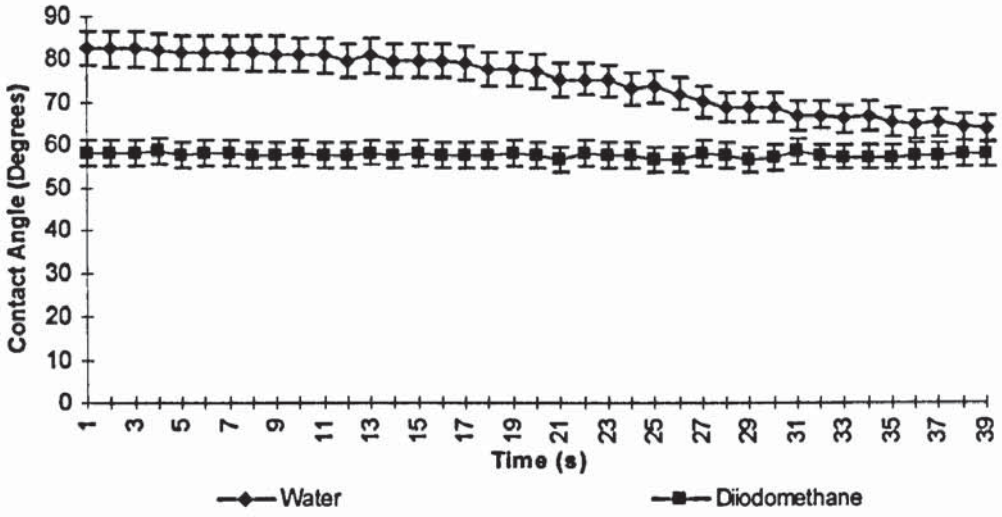


Figure 6.51 Contact angles against time, obtained from diiodomethane and water on a NaAMPS hydrogel gels (NaAMPS 40%, glycerol 28 % and water 32%) containing 10% PEG200 monomethacrylate.

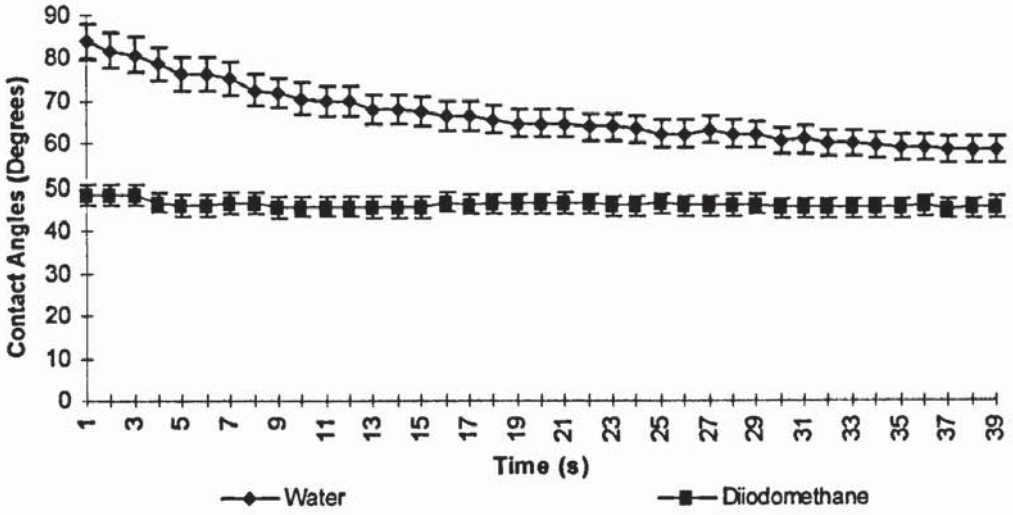


Figure 6.52 Contact angles against time, obtained from diiodomethane and water on a NaAMPS hydrogel gels (NaAMPS 40%, glycerol 28 % and water 32%) containing 20% PEG 200 monomethacrylate.

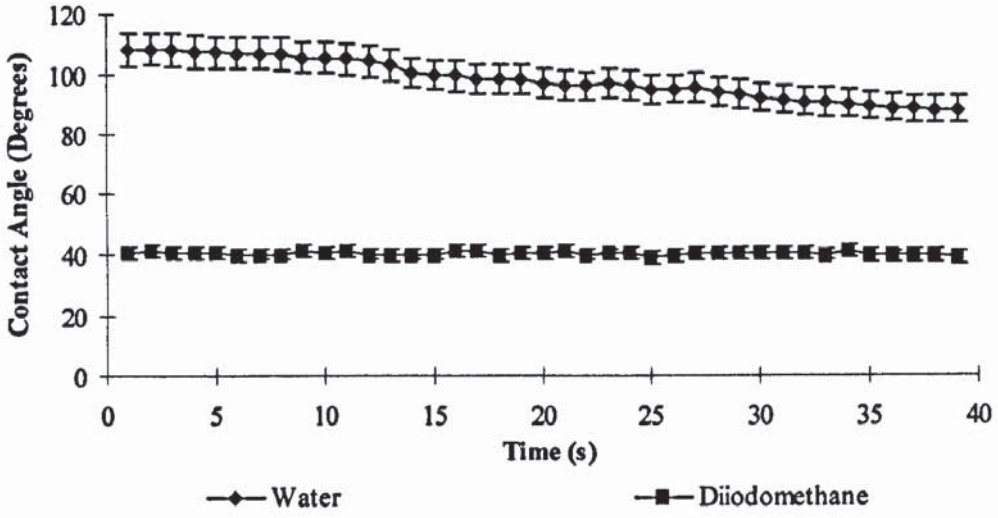


Figure 6.53 Contact angles against time, obtained from diiodomethane and water on a NaAMPS hydrogel gels (NaAMPS 40%, glycerol 28 % and water 32%) containing 30% PEG 200 monomethacrylate.

6.11 1 The effect of PEG 200 Monomethacrylate on Swelling

A hydrogel containing 10% PEG200 methacrylate was found to have the lowest water content angle indicating that it possesses the most polar surface of those investigated and

absorb water better due to the lower cross-link density. As the percentage PEG 200methacrylate was increased the water contact angle increased indicating the polar character of the surface was reduced and that less water was absorbed due to the high cross-link density. The presence of PEG200 methacrylate increased the hydrophobic content of the gel as indicated suggested by the lower diiodomethane contact angle as the proportion of PEG 200 monomethacrylate is increases. The latter hydrogel is very hydrophilic with a large capacity to absorb water and it can be seen from the graph that the contact angle of water decreases over time due to its interaction with the hydrogel, contrasting with diiodomethane where there is no deviation from the initial contact angle.

The swelling of these gels was determined by cutting out a disc of hydrogel, measuring its thickness with a micrometer and placing it on a laminated grid to measure its diameter. The area was calculated using the formula $A= \pi R^2$ and this was multiplied by the thickness to obtain the volume in mm^3.

PEG200 monomethacrylate (% Added)	Initial volume (mm^3)	volume increase after 1 hr (%)	Volume increase after 1 day (%)
0	831.3	1122	9331
10	488.4	1144	1144
20	467.6	674	674
30	409	158	158

Table 6.16 Gel compositions (w/w) used to test swelling.

The results in table 6.16 indicate that gels swell to completion after one hour when they contain PEG 200 monomethacrylate and that they continued to swell for a much longer period if they contained no PEG 200 monomethacrylate. As the percentage of PEG 200 monomethacrylate increased, the gels adhesiveness decreased. Only the 10% PEG 200 monomethacrylate gel would be suitable to use as a skin adhesive because the tack falls to an unacceptable level beyond this level of monomer. It was also noted that the gels with the higher amount of PEG 200 monomethacrylate were brittle and broke into fragments up on swelling.

6.12 Conclusion

Several ionic monomers were examined to evaluate their suitability for use as hydrophilic components in adhesive gels. NaAMPS was the most effective ionic monomer tested in terms of cohesive strength, followed by SPA which was marginally more adhesive but less cohesive. A range of compositions containing NaAMPS, water and glycerol were tested to observe which composition produced the most adhesive and cohesive gels The dynamic mechanical properties of the gels were tested and 10^3-10^5 Pa at 1-100 rad/s was identified as a good value for skin adhesive gels.

The addition of acrylic acid to the gels increased the peel strength by removing interfacial water and enhanced the rheological properties, shown by an increase in G'. This was as a result of intermolecular interactions. The addition of DM 137 increased peel strength by interacting with the hydrophobic lipids of the skin. Surface free energy measurements demonstrated that DM 137 acted at the surface of the hydrogel. Acrylic acid and DM 137 together enhanced the peel strength further as they acted at different sites. The adhesive surface was studied under the microscope and the gel containing DM 137 appeared to exhibit a biphasic surface giving hydrophilic and hydrophobic domains.

Water loss from gels were examined and it was noted that water loss increased with an increasing number of cures as expected, and most of the water was lost after the first few passes under the UV lamp. The percent total water loss is slightly higher from the gel containing 5% added water. The rate of water loss from the gel with 5% added water is slightly higher at first but levels off after subsequent passes.

The dynamic mechanical properties of a fundamental NaAMPS gel was studied to determine the effect of curing on the cohesive strength of the gel. With increased passes under the UV lamp, we can observe that the G', G'' and tan delta values increased the most between 5 and 10 passes, suggesting that the cohesive strength increased with curing to a greater extent at the onset than after subsequent passes beneath the UV lamp, denoting that for NaAMPS gels there is no requirement to pass the gels under the UV more than ten times to obtain a well cured gel with good cohesive strength.

The water content of a fundamental NaAMPS gel was increased to ascertain the effects on adhesion. As the water content increased the adhesion decreased, probably due to a reduced ability of the gel to remove interfacial water.

The adhesive hydrogels swell readily in water and this may present problems when used in a moist environment. Therefore, gels were produced containing PEG 200 monomethacrylate which were found to have completely swelled after an hour. As the percentage of PEG 200 monomethacrylate increased, the gels adhesiveness decreased. Above 10 % PEG 200 monomethacrylate gel would be too high to use as a skin adhesive because the tack is reduced too much for the applications required and the gels with the higher amount of PEG 200 monomethacrylate were brittle and broke into fragments on swelling.

Chapter 7

Conclusions and Proposals for Further Work

7.1 Conclusions

A patent review revealed that the first forms of polymer adhesion to the skin arose from a requirement to adhere a biomedical device, such as an electrode, to the skin by being pasted onto the body. This system was cumbersome and pain could be experienced when removing or repositioning the device and adhesive. Subsequent adhesives often contained multi-layers which were prone to de-layering or leaving residues on the skin after removal. The most recent bioadhesives are not sufficiently adhesive and/or lack cohesive strength. If the adhesive is being used for electrical stimulation and does not adhere properly, then burning of the skin may occur.

The ideal skin adhesive should not irritate the skin, must be sufficiently cohesive to be readily removable, should require no preparation of skin, be a good electrical conductor if conductance is required, should ideally give better skin contact and hence, give better electrical contact resulting in increased efficacy of defibrillation and finally the residual monomer present after polymerisation is preferred to be less than 3% for optimal biocompatibility.

Initially, non-adhesive hydrogels were investigated to determine fundamental properties of hydrogels, in particular their EWC and the effects the individual components had on the EWC. It was established using DSC that an increased EWC was due to an increase in freezing water. The results identified three contributing factors, each of which has an effect on the hydrophilicity and specific water binding characteristics of the gel networks.

The first factor is the level of high molecular weight hydrophilic cross-linking agent PEG DM. PEG 1000DM was found to be the optimal molecular weight of cross-linker tested as it produced non-brittle gels with high EWC. PEG DM of lower molecular weights produced gels with a high cross-link density and were too brittle. Higher molecular weight PEGs may produce gels with higher EWC with a possible reduction in mechanical strength. However, PEG 1000DM was sufficient for the purposes required here.

The second factor is the nature of the ionic hydrophilic group, in this instance the sulphonate groups of SPI and SPA appeared to make them the most hydrophilic.

However, all of the ionic monomers used were very hydrophilic.

The third factor is the effective concentration of the ionic hydrophilic group in the monomer repeat unit. All ionic monomers had a similar molecular incorporation of sulphonate groups, with SPI having a slight advantage over SPA because it has a marginally higher ratio of moles sulphonate groups per unit mass of monomer for the same number of ionic hydrophilic groups.

The good hydrophilicity of SPI per unit mass rendered it a good initial choice for use producing bioadhesive hydrogels. The high affinity that the gel has for water enhances the removal of moisture thereby reducing lubrication and therefore presenting an adhesive surface which adheres to the skin. The high proportion of freezing water is desirable for conduction as electrolytes are solvated within the aqueous portion of the polymer layer.

The bioadhesives must possess physical properties such as sufficient flexibility to conform to the contours of the adherend, a sufficiently high molecular weight and functional groups to promote hydrogen bonding. The cohesive force, a measure of its structural integrity, should be greater than its adhesive forces so that the adhesive can be removed from the substrate without leaving an unacceptable amount of residue.

Peel adhesion, an important characteristic of pressure-sensitive adhesives, was evaluated by measuring the tensional force required to remove the adhesive. The peel test was developed to test the adhesion of the gels and the 90 degree peel test proved to be better than the 180 degree peel test for the adhesives tested. This is because the 180 degree peel test gave a stop start effect which was enhanced by the angle of peel. The peel test is dependant on adhesion in addition to other factors such as viscoelastic properties of the adhesive, stiffness of the adherend, rate of separation, and temperature.

Four skin models were tested to determine their potential to be used as a skin alternative for testing adhesives, however none were outstanding. The main reasons for wanting an alternative to skin was to reduce patient to patient variability along with other factors such as described to minimise the inflammation response.

Scanning Electron Microscopy was performed on some commercially used adhesives and on hydrogels to correlate peel strength with cell removal and damage. Under the conditions used, as peel strength increased cell removal also increased. If the adhesive is adhered to the body for any length of time, and replaced with a fresh adhesive and the peel test repeated, it can be observed that dead skin cells are removed first followed by a few viable cells and finally none or very few viable cells are removed.

To make a skin adhesive, the water content was reduced and the ionic monomer was increased to elevate the gel's affinity for water. Water control is important. If the adhesive hydrogel is too water swollen it will lose its hydrophilic potential and will no longer be able to remove the boundary layer of moisture and become non-adhesive. If not enough water is present then the polymer chains are not efficiently released from their restraints to interpenetrate with the substrate matrix. The glycerol content is increased as it reduced evaporation and augmented the plasticity of the gel, and the cross-link level was reduced to produce compliance, but not to such an extent as to weaken the mechanical strength extensively. Ionic monomer, glycerol and water are the major components of many adhesive gels described in the patent literature.

Many ionic monomers were tested in a simple adhesive formulation and only NaAMPS and SPA showed good potential for use as an adhesive in this system. The gels were most adhesive at approximately 40% ionic monomer, 30% glycerol and 30% water. NaAMPS produced the most cohesive gel and this is due to the interaction of the amide group on one chain with the sulphonate group on another. SPA gels alone were insufficiently cohesive and had residue on the surface. SPA does not possess this amide group which is present in NaAMPS, therefore validating the effect of the amide group on enhancing cohesion. The gels containing SPA were more adhesive than NaAMPS gels, therefore a combination of SPA and NaAMPS was investigated to increase the cohesion of an SPA gel and to increase the adhesion of NaAMPS gel. A 7:3 ratio of NaAMPS:SPA was chosen. Other components were added to these simple monomer solution such as acrylic acid and DM 137 to enhance the gel properties.

When incorporated into NaAMPS hydrogels, the addition of acrylic acid reduced surface residues and enhanced cohesion. This was due to increased intermolecular forces within

the gel. The peel strength of the gel was increased by removing the interfacial water and presenting a moisture-absorbing surface. Acrylic acid was shown to operate within the gel by not altering the surface free energy significantly and by increased cohesion as shown by the increased dynamic-mechanical properties. Acrylamide and N-iso-propyl acrylamide were incorporated into separate gels, however they were not as effective as acrylic acid at increasing peel strength. One explanation is that the acrylamide and the N-isopropyl acrylamide are providing amide groups to the system which are already present in NaAMPS, therefore an inferior effect is observed. Additionally the hydroxyl group present in acrylic acid is small and polar and may be more efficient at promoting intermolecular bonding. N-iso-propyl acrylamide was more effective at increasing peel strength than acrylamide alone as N-iso-propyl acrylamide is more hydrophobic and interacts with the skin better.

The addition of DM 137 enhanced adhesion by increasing the hydrophobic interactions at the surface of the gel, which in turn interacted with the lipids in the skin. DM 137 was shown to act at the surface of the gel by decreasing the polar component of the surface energy of the gel and by not significantly enhancing the dynamic mechanical properties of the gel. When both DM 137 and acrylic acid were incorporated into the gel, peel strength was increased further and the effects of the components were complementary rather than contrasting, again supporting the evidence for the components acting at different locations.

NaAMPS:SPA hydrogels demonstrated similar results as the NaAMPS hydrogels however they were more adhesive but less cohesive than the NaAMPS hydrogels, shown by decreased dynamic mechanical properties and increased peel strength. This is due to the intermolecular interactions of NaAMPS being diluted by the addition of SPA to the system. The amide sulphonate interaction is not promoted by SPA.

7.2 Further Work

7.2.1 Further work inferred from work completed

Titrations were performed on ionic monomers in chapter 3 to determine their pK_a and pK_b values However, the potentiometric titration of the monomer solution may have been more beneficial in predicting performance of the ionic monomer in a hydrogel.

Acrylamide and N-iso-propyl acrylamide should be incorporated into SPA and NaAMPS:SPA based gels, since the acrylamide and the N-isopropyl acrylamide would provide amide groups to the system which are not present in SPA. As mentioned previously, NaAMPS gels are cohesive due to the sulphonate-amide interactions. Providing SPA with amide groups may enhance the cohesive properties of SPA gels and if this is true SPA gels alone may be cohesive enough not to require NaAMPS. SPA gels are more adhesive than NaAMPS gels therefore if SPA gels can be produced they may be more adhesive than NaAMPS gels.

7.2.2 Optimising the Properties of Bioadhesive Gels

Having established a good series of formulations which produced good skin adhesive hydrogels, it was important to enhance their properties to optimise the properties of the gels identified. Enhancing the properties of the gels may include the addition of buffer systems to prevent discolouration and/or hydrolysis and thereby increase their shelf life. Buffering systems should also prevent electrochemical burning by helping to prevent pH changes/shifts as a current is driven through pairs of hydrogel electrodes and avoid hydrolysis of the gel. Conductivity enhancers may also be added and include salts such as potassium chloride and sodium chloride (the human body uses these salts for conduction) as well as bactericidal and fungicidal agents to prevent infection.

Smart hydrogels are systems which change their properties as a result of changes in their structure, resulting from changes in their local environment. Properties such as volume, viscosity or conductivity may change in response to variations in temperature, pH or mechanical stress. Dramatic changes to polymer properties can be generated through

reversible changes to hydrogen, ionic and hydrophobic bonding patterns within the polymer network. These systems may enable the production of superior skin adhesives.

7.2.3 Investigation of Gel Toxicity

The hydrogels studies were produced from both toxic monomers and a toxic initiator. After polymerisation the gels should, however, be non-toxic. An experiment was performed to determine the toxicity of the gels by testing the solution in which a hydrogel had been previously stored and swollen in for 7 days. The freezing point of the solution was measured. The freezing point reduction below that of pure water (0°C) is a direct measure of the osmotic concentration. A 50 µl sample of solution was removed from the container holding the gel and the osmotic concentration measured on a CAMLAB automatic micro-osmometer. The freezing point was marginally below 0°C suggesting the sample is virtually pure water. However the gel swells so greatly that 78mm^2 of gel required 150ml of water to allow complete swelling with enough solution remaining to test. The dilution of possible toxins may be so great that it was not detected.

Further work should address the toxicological aspects of these hydrogels by use of high pressure liquid chromatography using a specific column which would allow detection of any toxins. This would involve the gel being swollen in liquid, for example methanol, and the liquid injected through the appropriate column. An alternative approach would be to try and grow cells upon the hydrogel. If the hydrogel supported cell growth it would be considered to be non-toxic. However, this is impractical as the gel would swell copiously in the cell growth medium.

7.2.4 Exploiting the uses of Adhesive Gels

Skin adhesive hydrogels are a fairly new area of biomedical technology and their potential has not fully been exploited. Hydrogels are very versatile and have the capacity to be adapted for numerous applications. There is an opportunity for these adhesives to be used in new areas for uses such as super-absorbents for absorbing urine in nappies.

Other possibilities could include wax strips to remove hair from legs as some gels in this thesis have been shown to remove hair from arms, non permanent adhesion of objects such as paper or cardboard similar to Post It notes and even insoles for shoes which would exploit the hydrogels ability to absorb moisture.

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Appendix 1

Non-Adhesive Gel Compositions and their Tensile and Water Structuring Figures

HPMC (%)	PEG 600DM (%)	SPE (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)
0.9	58.5	6.5	1	0	34.1	0	1
0.9	52	13	1	0	34.1	0	1
0.9	39	26	1	0	34.1	0	1
0.9	26	39	1	0	34.1	0	1
0.9	58.5	6.5	1	8.5	22.6	0	1
0.9	52	13	1	8.5	22.6	0	1
0.9	39	26	1	8.5	22.6	0	1
0.9	26	39	1	8.5	22.6	0	1
0.9	58.5	6.5	1	17	17.1	0	1
0.9	52	13	1	17	17.1	0	1
0.9	39	26	1	17	17.1	0	1
0.9	26	39	1	17	17.1	0	1
1.25	45	5	1	0	48.75	0	1
1.25	40	10	1	0	48.75	0	1
1.25	30	20	1	0	48.75	0	1
1.25	20	30	1	0	48.75	0	1

HPMC (%)	PEG 600DM (%)	SPE (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)
1.25	45	5	1	12.25	36.5	0	1
1.25	40	10	1	12.25	36.5	0	1
1.25	30	20	1	12.25	36.5	0	1
1.25	20	30	1	12.25	36.5	0	1
1.25	45	5	1	24.25	24.25	0	1
1.25	40	10	1	24.25	24.25	0	1
1.25	30	20	1	24.25	24.25	0	1
1.25	20	30	1	24.25	24.25	0	1

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	Tensile Strength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
46	20	26	0.9	8	8	3
47	20	27	0.7	6.7	10	3
49	24	25	0.4	4.9	7	3
54	26	28	0.1	1	11	3
47	18	29	0.2	9.5	5	3
49	19	30	0.2	8	5	3
49	22	27	0.16	7	8	3
52	24	28	0.1	6.5	13	3
47	20	27	0.2	8	6	3
48	24	24	0.2	7.5	8	3
50	24	26	0.15	6	8	3
54	24	30	0.1	5	9	3
56	18	38	0.7	6	14	5
58	18	40	0.8	5.6	17	5
61	20	41	0.4	2.7	15	5
59	16	43	0.4	2	16	5

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	Tensile Strength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
54	13	41	0.4	5	9	5
56	15	41	0.3	4.2	10	5
57	14	43	0.3	3	8	5
58	15	43	0.2	2.5	9	5
57	14	43	0.3	2.9	7	5
59	13	46	0.2	1.5	7	5
59	14	45	0.2	2.2	10	5
60	15	45	0.15	2	9	5

* The optical clarity scale ranges from 1-5, with 1 being transparent and non-cloudy and 5 being opaque.

HPMC (%)	PEG 1000DM (%)	SPE (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)
1.25	45	5	1	0	48.75	0	1
1.25	40	10	1	0	48.75	0	1
1.25	30	20	1	0	48.75	0	1
1.25	20	30	1	0	48.75	0	1
1.25	45	5	1	12.25	36.5	0	1
1.25	40	10	1	12.25	36.5	0	1
1.25	30	20	1	12.25	36.5	0	1
1.25	20	30	1	12.25	36.5	0	1
1.25	45	5	1	24.25	24.25	0	1
1.25	40	10	1	24.25	24.25	0	1
1.25	30	20	1	24.25	24.25	0	1
1.25	20	30	1	24.25	24.25	0	1
1.9	22.5	2.5	1	0	73.1	0	1
1.9	20	5	1	0	73.1	0	1
1.9	15	10	1	0	73.1	0	1
1.9	10	15	1	0	73.1	0	1

HPMC (%)	PEG 1000DM (%)	SPE (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)
1.9	22.5	2.5	1	18.35	54.75	0	1
1.9	20	5	1	18.35	54.75	0	1
1.9	15	10	1	18.35	54.75	0	1
1.9	10	15	1	18.35	54.75	0	1
1.9	22.5	2.5	1	36.55	36.55	0	1
1.9	20	5	1	36.55	36.55	0	1
1.9	15	10	1	36.55	36.55	0	1
1.9	10	15	1	36.55	36.55	0	1

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	Tensile Strength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
61	21	39	0.6	4.6	14	3
61	28	33	0.5	4.1	15	3
60	20	40	0.4	3.2	14	3
61	14	47	0.3	2.1	13	3
61	23	38	0.5	5.6	9	3
62	28	34	0.45	5.2	9	3
64	25	39	0.3	3.2	9	3
60	11	49	0.13	2.6	6	3
59	23	36	0.5	4.8	10	3
61	23	38	0.4	4.2	9	3
61	18	43	0.2	2.4	9	3
61	13	48	0.13	1.4	10	3
73	25	48	0.3	1.2	22	5
72	26	46	0.2	1	24	5
73	32	41	0.2	1	24	5
75	28	47	0.18	0.7	25	5

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	Tensile Strength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
73	31	42	0.3	1	27	5
72	30	42	0.26	1.3	20	5
72	29	43	0.24	1.1	21	5
74	31	43	0.16	0.6	26	5
73	30	43	0.2	1	19	5
75	28	47	0.3	1.2	23	5
74	31	43	0.17	1	18	5
74	29	45	0.5	2.5	26	5

* The optical clarity scale ranges from 1-5, with 1 being transparent and non-cloudy and 5 being opaque.

HPMC (%)	PEG1000DM (%)	SPA (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Igracure184 (% added)
0.9	58.5	6.5	1	0	34.1	0	1
0.9	52	13	1	0	34.1	0	1
0.9	39	26	1	0	34.1	0	1
0.9	26	39	1	0	34.1	0	1
0.9	58.5	6.5	1	8.5	25.6	0	1
0.9	52	13	1	8.5	25.6	0	1
0.9	39	26	1	8.5	25.6	0	1
0.9	26	39	1	8.5	25.6	0	1
0.9	58.5	6.5	1	17	17.1	0	1
0.9	52	13	1	17	17.7	0	1
0.9	39	26	1	17	17.7	0	1
0.9	26	39	1	17	17.7	0	1
1.25	45	5	1	0	48.75	0	1
1.25	40	10	1	0	48.75	0	1
1.25	30	20	1	0	48.75	0	1
1.25	20	30	1	0	48.75	0	1

HPMC (%)	PEG1000DM (%)	SPA (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Igracure184 (% added)
1.25	45	5	1	12.25	36.5	0	1
1.25	40	10	1	12.25	36.5	0	1
1.25	30	20	1	12.25	36.5	0	1
1.25	20	30	1	12.25	36.5	0	1
1.25	45	5	1	24.25	24.25	0	1
1.25	40	10	1	24.25	24.25	0	1
1.25	30	20	1	24.25	24.25	0	1
1.25	20	30	1	24.25	24.25	0	1
1.9	22.5	2.5	1	0	73.1	0	1
1.9	20	5	1	0	73.1	0	1
1.9	15	10	1	0	73.1	0	1
1.9	10	15	1	0	73.1	0	1
1.9	22.5	2.5	1	18.35	54.75	0	1
1.9	20	5	1	18.35	54.75	0	1
1.9	15	10	1	18.35	54.75	0	1
1.9	10	15	1	18.35	54.75	0	1

HPMC (%)	PEG1000DM (%)	SPA (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Igracure184 (% added)
1.9	22.5	2.5	1	36.55	36.55	0	1
1.9	20	5	1	36.55	36.55	0	1
1.9	15	10	1	36.55	36.55	0	1
1.9	10	15	1	36.55	36.55	0	1

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	Tensile Strength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
57	21	36	0.6	7.3	8.5	1
62	28	34	0.7	6.7	10	1
66	25	41	0.3	5.1	6.5	1
72	25	47	0.3	3.1	8.6	1
58	28	30	0.7	6.5	10.4	2
61	30	31	0.6	6.1	9.8	2
68	32	36	0.2	3.9	7.1	2
74	37	37				2

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	Tensile Strength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
54	25	29	0.5	5.3	8.9	3
62	30	32	0.5	4.7	10.2	3
70	30	40	0.3	3.7	7.5	3
75	26	49				3
63	22	41	0.5	4.4	11.9	1
65	32	33	0.4	4.4	10.5	1
71	33	38	0.4	3.8	9.5	1
75	25	50	0.3	3.1	10.3	1
62	29	33	0.6	4	17.8	2
64	30	34	0.6	3.9	16	2
67	32	35	0.4	2.7	14.3	2
73	29	36	0.4	1.5	21.6	2
67	32	35	0.3	2.7	10.7	3
70	29	41	0.4	3.4	11	3
73	28	45				3
81	30	51				3

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	Tensile Strength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
75	29	46	0.3	1	24.3	1
78	24	54	0.3	1	31.1	1
84	22	62	0.1	0.8	16.8	1
86	17	69	0.1	0.7	14.8	1
78	13	65	0.2	1.7	9.3	2
80	21	59	0.2	1.3	10.6	2
84	17	67	0.1	0.9	14.2	2
88	17	71	0.1	0.8	18.3	2
78	26	51	0.2	0.8	18.4	3
82	22	63	0.1	0.6	19.5	3
83	18	65	0.1	0.6	16.2	3
85	17	68	0.1	0.5	17.1	3

* The optical clarity scale ranges from 1-5, with 1 being transparent and non-cloudy and 5 being opaque.

HPMC (%)	PEG 1000DM (%)	SPI (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Igracure 184 (% added)
0.9	58.5	6.5	1	0	34.1	0	1
0.9	52	13	1	0	34.1	0	1
0.9	39	26	1	0	34.1	0	1
0.9	26	39	1	0	34.1	0	1
0.9	58.5	6.5	1	8.5	25.6	0	1
0.9	52	13	1	8.5	25.6	0	1
0.9	39	26	1	8.5	25.6	0	1
0.9	26	39	1	8.5	25.6	0	1
0.9	58.5	6.5	1	17	17.1	0	1
0.9	52	13	1	17	17.7	0	1
0.9	39	26	1	17	17.7	0	1
0.9	26	39	1	17	17.7	0	1
1.25	45	5	1	0	48.75	0	1
1.25	40	10	1	0	48.75	0	1
1.25	30	20	1	0	48.75	0	1
1.25	20	30	1	0	48.75	0	1

HPMC (%)	PEG 1000DM (%)	SPI (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Igracure 184 (% added)
1.25	45	5	1	12.25	36.5	0	1
1.25	40	10	1	12.25	36.5	0	1
1.25	30	20	1	12.25	36.5	0	1
1.25	20	30	1	12.25	36.5	0	1
1.25	45	5	1	24.25	24.25	0	1
1.25	40	10	1	24.25	24.25	0	1
1.25	30	20	1	24.25	24.25	0	1
1.25	20	30	1	24.25	24.25	0	1
1.9	22.5	2.5	1	0	73.1	0	1
1.9	20	5	1	0	73.1	0	1
1.9	15	10	1	0	73.1	0	1
1.9	10	15	1	0	73.1	0	1
1.9	22.5	2.5	1	18.35	54.75	0	1
1.9	20	5	1	18.35	54.75	0	1
1.9	15	10	1	18.35	54.75	0	1
1.9	10	15	1	18.35	54.75	0	1

HPMC (%)	PEG 1000DM (%)	SPI (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Igracure 184 (% added)
1.9	22.5	2.5	1	36.55	36.55	0	1
1.9	20	5	1	36.55	36.55	0	1
1.9	15	10	1	36.55	36.55	0	1
1.9	10	15	1	36.55	36.55	0	1

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	TensileStrength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
57	21	36	0.6	6.1	10.1	1
63	30	33	0.5	4.8	11	1
71	25	46	0.2	2.4	8.7	1
80	22	58	0.1	0.9	6.5	1
60	24	36	0.5	4.9	9.4	2
64	31	33	0.5	4.6	11	2
68	27	41	0.2	3.3	6.9	2
74	24	50	0.1	1.5	2.4	2

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	TensileStrength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
59	23	36	0.6	5.7	11.3	3
63	29	34	0.5	5.4	8.7	3
68	27	41	0.1	2.8	8.3	3
74	19	55	0.6	1.6	4.9	3
69	31	38	0.4	3.8	11.5	1
70	29	41	0.3	3	10.7	1
74	24	50	2.1	0.2	11	1
81	20	61	0.1	1	10.9	1
66	26	40	0.4	2.8	13.9	2
69	31	38	0.3	2.3	12	2
75	25	50	0.2	1.9	10.8	2
81	21	61	0.1	0.1	11	2
69	32	37	0.4	3.2	11.4	5
70	32	38	0.3	2.2	11.5	5
77	25	52	0.1	1.7	7.8	5
83	22	61	0.1	0.1	8.7	5

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	TensileStrength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
78	26	52	0.2	0.55	31.6	2
81	24	57	0.2	0.48	39.9	2
85	18	67	0.08	0.31	25.8	2
89	19	70	0.06	0.12	38	2
78	23	55	0.11	0.44	24.2	2
82	22	60	0.06	0.31	15.5	2
86	21	65				2
89	21	68				2
79	26	53	0.2	0.72	25.2	5
83	23	60	0.14	0.58	22.5	5
86	13	73	0.07	0.34	20.2	5
91	12	79	0.04	0.33	13.8	5

* The optical clarity scale ranges from 1-5, with 1 being transparent and non-cloudy and 5 being opaque.

HPMC (%)	PEG 1000DM (%)	SPV (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Igracure 184 (% added)
1.9	22.5	2.5	1	0	73.1	0	1
1.9	20	5	1	0	73.1	0	1
1.9	15	10	1	0	73.1	0	1
1.9	10	15	1	0	73.1	0	1
1.9	22.5	2.5	1	36.55	36.55	0	1
1.9	20	5	1	36.55	36.55	0	1
1.9	15	10	1	36.55	36.55	0	1
1.9	10	15	1	36.55	36.55	0	1

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	TensileStrength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
81	30	51	0.22	0.61	33.5	5
84	24	60	0.1	0.19	51.3	5
84	24	60	0.03	0.17	14	5
86	17	69	0.03	0.17	14	5
75	26	49	0.22	1.14	19.1	3
82	32	50	0.13	0.64	20.4	3
83	21	62				3
86	10	76				3

* The optical clarity scale ranges from 1-5, with 1 being transparent and non-cloudy and 5 being opaque

HPMC (%)	PEG 1000DM (%)	NaAMPS (%)	M bis A (% added)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)
1.9	22.5	2.5	1	0	73.1	0	1
1.9	20	5	1	0	73.1	0	1
1.9	15	10	1	0	73.1	0	1
1.9	10	15	1	0	73.1	0	1
1.9	22.5	2.5	1	36.55	36.55	0	1
1.9	20	5	1	36.55	36.55	0	1
1.9	15	10	1	36.55	36.55	0	1
1.9	10	15	1	36.55	36.55	0	1

EWC (%)	Non-Freezing Water (%)	Freezing Water (%)	Tensile Strength (MPa)	Modulus (MPa)	Elongation (%)	Optical Clarity *
78	27	51	0.29	0.88	30.1	5
80	25	55	0.23	0.95	23.2	5
84	20	64	0.17	0.77	22	5
87	17	70	0.1	0.66	12.6	5
77	20	57	0.2	0.9	21.5	4
80	20	60	0.18	0.93	19.9	4
84	20	64	0.16	0.88	17.6	4
87	16	71	0.06	0.59	8	4

- The optical clarity scale ranges from 1-5, with 1 being transparent and non-cloudy and 5 being opaque

Appendix 2

Adhesive Gel Compositions Containing Interpenetrants and their Quality Values

SPI (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)	HPMC (%)	PEG 1000DM (%)	M bis A (%added)	Comparison of adhesion	Gel quality
34	40	26	0	1	2	0.5	1	4	1
34	40	26	0	1	2	1	1	4	1
34	40	26	0	1	2	2.5	1	1	2
34	40	26	0	1	2	5	1	0	3
34	40	26	0	1	2	10	1	0	3

SPI (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)	HPMC (%)	PEG 1000DM (%)	M bis A (%added)	Comparison of adhesion	Gel quality
34	40	26	0	1	2	1	0.1	5	1
34	40	26	0	1	2	1	0.2	5	1
34	40	26	0	1	2	1	0.3	4	2
34	40	26	0	1	2	1	0.4	4	3
34	40	26	0	1	2	1	0.5	4	4
34	40	26	0	1	2	1	0.6	4	4
34	40	26	0	1	2	1	0.7	3	4
34	40	26	0	1	2	1	0.8	3	4
34	40	26	0	1	2	1	0.9	3	5
34	40	26	0	1	2	1	1	2	5

Monomer	Monomer (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure 184 (% added)	HPMC (%)	PEG1000 DM (%)	M bis A (%added)
SPA	34	40	26	0	1	2	1	0.6
SPE	34	40	26	0	1	2	1	0.6
SPI	34	40	26	0	1	2	1	0.6
SPP	34	40	26	0	1	2	1	0.6
SPV	34	40	26	0	1	2	1	0.6
Na AMPs	34	40	26	0	1	2	1	0.6

Comparison of adhesion	Gel description
1	SPA formed a cloudy gel which crystallised over night to leave a dry rubbery polymer
1	SPE formed a nearly transparent, good but non-adhesive gel
4	SPI formed a good, nearly transparent, adhesive gel
3	SPP formed a white, satisfactory gel
5	SPV formed a great, yellowish, nearly transparent adhesive gel especially when left over night
1	Na AMPS formed a cloudy, non-adhesive gel

SPV (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure184 (added %)	HPMC (%)	PEG 1000 DM (%)	M bis A (added %)	Comparison of adhesion	Gel quality
30	40	30	0	1	2	1	0.6	5	3
31	40	29	0	1	2	1	0.6	5	3
32	40	28	0	1	2	1	0.6	4	4
33	40	27	0	1	2	1	0.6	4	4
34	40	26	0	1	2	1	0.6	3	5
35	40	25	0	1	2	1	0.6	3	5
36	40	24	0	1	2	1	0.6	3	5
37	40	23	0	1	2	1	0.6	3	5
38	40	22	0	1	2	1	0.6	2	5
39	40	21	0	1	2	1	0.6	1	5
40	40	20	0	1	2	1	0.6	1	5

SPE (%)	SPV (%)	Glycerol (%)	NaCl (%)	Irgacure184 (added %)	HPMC (%)	PEG1000 DM (%)	M bis A (added %)	Comparison of adhesion	Gel quality
15	15	40	0	1	2	1	0.6	5	4
15.5	15.5	40	0	1	2	1	0.6	5	4
16	16	40	0	1	2	1	0.6	5	4
16.5	16.5	40	0	1	2	1	0.6	5	5
17	17	40	0	1	2	1	0.6	5	5
17.5	17.5	40	0	1	2	1	0.6	5	5
18	18	40	0	1	2	1	0.6	5	5
18.5	18.5	40	0	1	2	1	0.6	5	5
19	19	40	0	1	2	1	0.6	5	4
19.5	19.5	40	0	1	2	1	0.6	5	4
20	20	40	0	1	2	1	0.6	5	4

SPI (%)	Glycerol (%)	Water (%)	NaCl (%)	Irgacure184 (added %)	HPMC (%)	PEG 1000 DM (%)	M bis A (added %)	Comparison of adhesion	Gel quality
30	40	30	0	1	2	1	0.6	5	2
31	40	29	0	1	2	1	0.6	5	2
32	40	28	0	1	2	1	0.6	5	3
33	40	27	0	1	2	1	0.6	5	3
34	40	26	0	1	2	1	0.6	5	3
35	40	25	0	1	2	1	0.6	5	3
36	40	24	0	1	2	1	0.6	5	4
37	40	23	0	1	2	1	0.6	5	4
38	40	22	0	1	2	1	0.6	5	4
39	40	21	0	1	2	1	0.6	5	4
40	40	20	0	1	2	1	0.6	5	5
41	40	19	0	1	2	1	0.6	5	4
42	40	18	0	1	2	1	0.6	4	3
43	40	17	0	1	2	1	0.6	4	2
44	40	16	0	1	2	1	0.6	4	2
45	40	15	0	1	2	1	0.6	3	1

Interpenetrant	Weight gain from original sample after 1 day	Weight gain from original sample after 2 days	Weight gain from original sample after 6 days
HPMC	0.12g	0.18g	0.02g
Gum Xanthan	0.13g	0.20g	0.01g
Gum Karaya	0.11g	0.16g	0.02g
Gum Locus Bean	0.11g	0.15g	0.03g

SPI : Water	Weight gain from original sample after 1 day	Weight gain from original sample after 5 days
2.5 : 0.5	0.12g	0.02g
2.6 : 0.4	0.15g	0.01g
2.7 : 0.3	0.11g	0.00g
2.8 : 0.2	0.17g	0.19g
2.9 : 0.1	0.24g	0.04g
3.0 : 0.0	0.32g	0.06g

Appendix 3

Peel Strengths

Gel	Substrate	Run	Peel Strength (N)	Width (mm)	Peel Strength (N/mm)
NaAMPS	Rubber	1	0.284	25	0.01136
NaAMPS	Rubber	2	0.219	25	0.00876
NaAMPS	Rubber	3	0.21	25	0.0084
NaAMPS	Skin	1	7.44	25	0.2976
NaAMPS	Skin	2	6.19	25	0.2476
NaAMPS	Skin	3	6.13	25	0.2452
NaAMPS	Metal	1	12.98	25	0.5192
NaAMPS	Metal	2	11.91	25	0.4764
NaAMPS	Metal	3	11.15	25	0.446
SPA	Rubber	1	1.64	25	0.0656
SPA	Skin	1	13.31	25	0.5324
SPA	Metal	1	16.67	25	0.6668

Appendix 4

Properties of Gels made from NaAMPS, Glycerol and Water

NaAMPS (%)	Glycerol (%)	Water (%)	PI/Xl (%)	Description
20	10	70	0.1	Non-cohesive
20	20	60	0.1	Non-cohesive
20	60	20	0.1	Non-cohesive
25	25	50	0.1	Non-cohesive
25	50	25	0.1	Non-cohesive
30	20	30	0.1	Poor cohesion
30	30	40	0.1	Poor cohesion
30	40	30	0.1	Poor cohesion
30	50	20	0.1	Poor cohesion
37	29	34	0.1	Good cohesion and adhesion
40	10	50	0.1	Good cohesion and adhesion
40	20	40	0.1	Good cohesion and adhesion
40	31	29	0.1	Good cohesion and adhesion

40	30	30	0.1	Good cohesion and adhesion
40	40	20	0.1	NaAMPS did not dissolve
40	60	0	0.1	Non-cohesive
50	10	40	0.1	Non-cohesive
50	20	30	0.1	NaAMPS did not dissolve
50	30	20	0.1	NaAMPS did not dissolve
50	50	0	0.1	Non-cohesive
60	20	20	0.1	NaAMPS not dissolving