ASTON UNIVERSITY

SKIN ADHESIVE HYDROGELS FOR THE TOPICAL DELIVERY OF ACTIVE AGENTS

By

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THESIS SUMMARY

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This thesis illustrates the development of tailor-made, partially hydrated skin adhesive hydrogels as a vehicle for the topical delivery of moisturising agents. Maintaining an optimum hydration level of the stratum corneum ensures that the barrier properties of the skin are preserved.

An unsaturated ionic monomer 2-acrylamido-2-methylpropanesulfonic acid sodium salt, glycerol, water, a photoinitiator Irgacure 184 and crosslinker Ebacryl II facilitated the production of monophasic sheet skin adhesives using photopolymerisation. The exploration and modification of the hydrogel components coupled with their influence on the adhesive and dynamic mechanical behaviour led to the development of novel monophasic and biphasic hydrogels.

Biphasic pregels comprising of a hydrophobic monomer (epoxidised soybean oil acrylate, lauryl acrylate or stearyl acrylate) micellised with a non ionic surfactant Tween 60 allowed a homogeneous distribution throughout a predominantly hydrophilic phase (2-acrylamido-2-methylpropanesulfonic acid sodium salt, 4-acryloylmorpholine, glycerol and water). Further development of biphasic hydrogel technology led to the incorporation of preformed commercial O/W emulsions (Acronal, Flexbond 150, DM137 or Texicryl 13056WB) allowing the hydrophobic component to be added without prior stabilisation.

The topical release of moisturising agents 2–pyrrolidone-5-carboxylic acid, lactobionic acid and d-calcium pantothenate results in the deposition onto the skin by an initial burst mechanism. The hydration level of the stratum corneum was measured using a Corneometer CM 825, Skin Reader MY810 or FT-ATR. The use of hydrophilic actives in conjunction with lipophilic agents for example Vitamin E or Jojoba oil provided an occlusive barrier, which reduced the rate of transepidermal water loss. The partition coefficients of the release agents provided invaluable information which enabled the appropriate gel technology to be selected.

In summary the synthetic studies led to the understanding and generation of transferable technology. This enabled the synthesis of novel vehicles allowing an array of actives with a range of solubilities to be incorporated.

Keywords: skin adhesive hydrogels, monophasic, biphasic, topical delivery, skin moisturisation

For My Family

"The beginning of knowledge is the discovery of something we do not understand."

(Frank Herbert, 1920 – 1986)

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List of Abbreviations

Abs	Absorbance
α	Alpha
ATR	Attenuated Total Reflectance
BIA	Bioelectic Impedance Analysis
cm	Centimeters
°C	Degrees centigrade
DVS	Dynamic vapour sorption
EWC	Equilibrium water content
FT-ATR	Fourier Transform Attenuated Total Reflectance
g	Grams
G'	Elastic modulus
G''	Viscous modulus
HLB	Hydrophile lipophile balance
Hz	Hertz
H_2 bonding	Hydrogen bonding
IR	Infrared
K_{ow}	Octanol water partition coefficient
MCG plate	Melinex coated glass plate
ml	Millilitre
mm	Millimetre
N	Newton
NMF	Natural moisturising factor
O/W	Oil in water
Pa	Pascal
%	Percentage
PI	Photoinitiator
revs/min	Revolutions per minute
SC	Stratum corneum
Tan δ	Tan delta
TEWL	Trans epidermal water loss
TS	Tape strip

3D	Three dimensional
UV	Ultraviolet
w/w	Weight /weight ratio
XL	Crosslinker
>	Greater than
<	Less than

Chemical abbreviations are available in chapter 2 (table 2.1).

Chapter 1

Introduction

1 Introduction

1.1 Hydrogel structure

Hydrogels are three dimensional crosslinked hydrophilic polymer networks (Nicholson J.W., 2002). They possess the ability to imbibe large quantities of water or biological fluids without dissolving (Peppas N.A 2004). Hydrophilicty of these gels is attributed to the presence of hydroxy, carbonyl, amide or sulfonic groups along the polymer chain. Crosslinks formed by covalent bonds, electrostatic, hydrophobic or dipole-dipole interactions prevent the gel from dissolving fully. The structural and physical integrity of the gels are a result of these interactions.

Research on hydrogels started in 1960 with a landmark hydrogel paper based on poly(2-hydroxyethyl methacrylate) known as poly HEMA. Wichterle and Lim suggested that it was a biocompatible synthetic material. This resulted in the development of the various applications of hydrogels for example biocompatible polymers and novel drug delivery systems (Wichterle et al 1960). Ratner and Hoffman suggested that the physical properties of hydrogels resembled those of living tissue more than other classes of synthetic biomaterials. Their relatively high water content and soft rubbery consistency give a strong superficial resemblance to soft living tissue (Hoffman 2002). A wide variety of materials can be used to prepare the hydrogels, including naturally originating materials (proteins such as collagen, polysaccharides such as chitosan or hyaluronic acid) which require modification and synthetic chemicals as shown in figure 1.1.

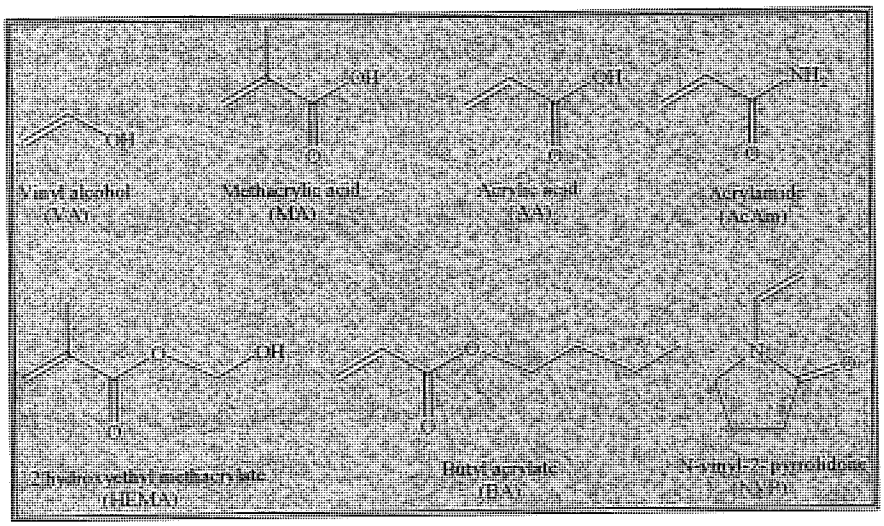


Figure 1.1 Monomers used in the synthesis of hydrogels

The network can be composed of one type of hydrophilic monomer forming homopolymers or two types of monomer forming copolymers (Peppas et al 2000). Hydrogels can be classified according to the nature of the side group. Neutral gels possess chains with no side charge and ionic gels have either negatively or positively charged side groups (Wang C et al 2001). Morphology is another category used to classify the structure of gels. Amorphous gels possess random polymer chains, semi crystalline gels contain denser regions of ordered polymer chains and hydrogen bonded gels have a three dimensional polymer network held together through this interaction (Peppas et al 2000). The shape of a hydrogel is maintained by the balance between the osmotic forces, originating from the entry of the water into the polymer and cohesive forces exerted by the polymer chains which resist expansion, also known as the elastic network retraction force.

1.2 Chemical and Physical Properties of Hydrogels

1.2.1 Water in Hydrogels

Water has numerous roles within a hydrogel as a plasticiser, a transport medium within the polymer matrix for dissolved species for example oxygen and a "bridge" between the different surface energies of synthetic polymers. Water absorbed by a hydrogel network structure contributes to the mechanical and physical properties of the gel (Corkhill P.H. et al, 1987). The equilibrium water content (EWC) gives a quantitative evaluation of the water content of a gel and is expressed as the ratio of the weight of water in the hydrogel to the weight of water at equilibrium hydration (equation 1.1):

$$\text{EWC (\%)} = \frac{[(\text{hydrated weight} - \text{dry weight})]}{\text{hydrated weight}} \times 100 \qquad (1.1)$$

Water present in a hydrogel exists between two extreme states as shown in figure 1.2. Strong association between water and a polymer through hydrogen bonding is known as

bound or non freezing water. If the water has a greater degree of mobility and remains unaffected by the polymeric environment it is referred to as free or unbound water.

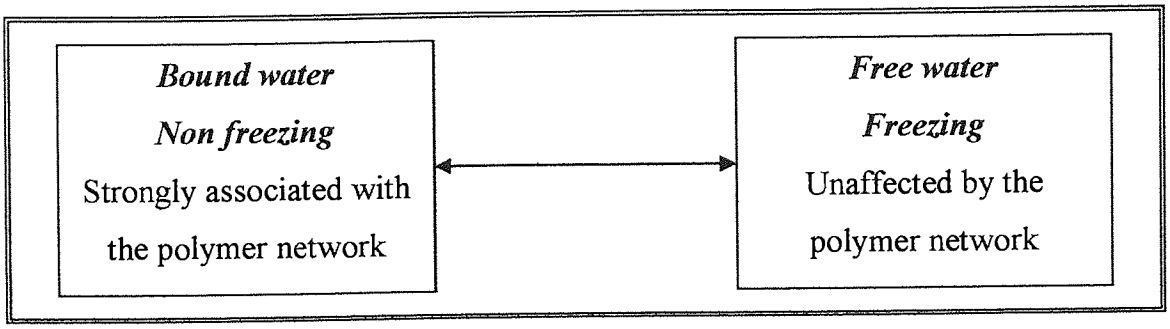


Figure 1.2 Classification of the bound and free water in hydrogels (Corkhill et al 1987)

The different types of water present in hydrogels can be quantified and characterised by using differential scanning calorimetry (DSC).The absorption characteristics of water in hydrophilic polymers vary in accordance to the following factors:

Nature of the hydrophilic groups

Water molecules interact more strongly with the polar groups within the polymer matrix than the non polar groups in the form of ion-dipole, dipole-dipole or hydrogen bonding. The distribution of bound to free water is affected by the polarity of the functional groups. For example ionic functional groups and strong acids will bind more strongly to the water compared to non ionic polar groups (on the basis of the number of water molecules per functional group). Amide groups have a stronger binding power compared to hydroxyl or ether groups. Generally higher degrees of hydration are achieved for those hydrogels synthesised from more hydrophilic based monomers or polymers.

Crosslink density of the polymer matrix

Increases in the crosslink density result in the formation of rigid structures with a decrease in the water content of the hydrogel. The amount of free water decreases due to the reduced mobility of the water molecules whilst the relative amounts of bound water increase.

Hydrophobic character

Hydrogen bonding is largely responsible for the amount of bound water. Both interchain and intermolecular hydrogen bonding reduce the number of sites available for water and diminishes the amount of bound water.

The type of water in the hydrogel affects the overall permeation of nutrients into the gel and cellular products out of the gel. Water in hydrogels can be characterised using DSC and NMR spectroscopy.

1.2.2 Plasticisers

A plasticiser is an additive which makes a polymer material more flexible (by decreasing the glass transition temperature) and more malleable (Billmeyer F.W. Jr, 1984). Generally there is a reduction in the cohesive intermolecular forces along the polymer chain. In hydrogels both water and glycerol are used to placticise the gel. There are two principle methods for softening a polymer (Stevens M.P, 1990):

- Internal plasticisation

The monomer is chemically modified prior to polymerisation. Implementing side chain grafting tends to increase the flexibility of the material.

- External plasticisation

The addition of a suitable plasticising agent (post polymerisation) is a desired solution and reduces overall costs. The plasticiser interacts physically and acts as a solvent for the polymer. There are two groups of external plasticiser (Billmeyer F.W. Jr, 1984):
Primary plasticiser – which causes an increase in softness and elongation to take place
Secondary plasticiser – which enhances the performance of the primary plasticiser.
Three major theories, described below, explain how plasticisers alter polymer properties both by internal and external plasticisation (Wypych G., 2003, Barlow F., 1993).

- The Lubrication Theory

This theory explains the effect of an external plasticiser on a polymer. An unplasticised polymer is rigid since friction exists between its chains, binding them into a network. Heating results in the weakening of bonds which allows smaller plasticiser molecules to

slide between the chains. Upon cooling the plasticiser molecules shield the chains from each other thus preventing the reformation of the rigid network.

- The Gel Theory

This is an extension of the lubrication theory. It proposes that the plasticiser molecules break up the polymer-polymer interaction by getting between the chains and the interaction sites from the polymer molecules.

- The Free Volume Theory

This is an extension of both the lubrication and gel theories and explains both internal and external lubrication. The free volume of a polymer is a measure of the internal space available for the movement of the polymer chains. Plasticisers increase the free volume of the polymer, maintaining it as the mixture is cooled. This prevents interactions between neighbouring polymer chains. Motion of the chain, chain ends or attached side chains increase the free volume of the polymer. A plasticiser has a lower molecular weight than the polymer. It has the ability to impart a greater free volume per volume of material since there is an increase in the proportion of end groups and the plasticiser has a glass transition temperature lower than that of the polymer.

1.2.3 Glass Transition Temperature (T_g)

The phenomenon of glass transition is observed in the amorphous region of polymers (Cowie J.M., 1991, Young R.J. et al., 1991). It occurs at a defined temperature when the bulk material ceases to be brittle and glassy in nature. It exhibits less rigid and more rubbery characteristics. Physical properties including the mechanical damping, refractive index and the electrical properties change profoundly at the T_g of the material. These properties are dependent on the relative degree of freedom within a given polymeric material. The glass transition can be understood by considering the changes that occur at this temperature. When a material is heated to this point and beyond the molecular rotation around a single bond becomes significantly easier. Numerous factors affect how the molecular rotations take place. An increase or reduction in the mobility of a polymer varies depending upon the molecular features. This results in different T_g values. Restrictions in the molecular mobility arise when polymer molecules interact, altering the

T_g of the polymeric material. There are a number of factors which are known to influence the glass transition temperature:

- Plasticisers

The incorporation of low molar mass chemicals decrease the interchain forces, reducing the Tg value.

- Crosslinking & branching

A crosslinked polymer with a low concentration of chain ends reduces the free volume and a subsequent increase in the T_g is observed. Branching increases the free volume of the polymer which results in the reduction of the T_g value.

- Hydrogen Bonding

This type of bonding, between the polymer chains, results in a decrease in the rotational freedom from the intermolecular bonding and increases the T_g value.

- Relative molar mass

Polymers of higher molar mass have less mobility and more restrictions on their overall molecular freedom than polymers of lower molecular mass which causes a raised Tg value.

- Polarity

Chloro and hydroxyl groups are comparable in size to methyl groups. However, more polar groups results in a higher T_g value due to an increase in the dipole-dipole interaction.

- Pendant groups

The presence of pendant groups on the polymer backbone increases the rotational energy and consequently the T_g value increases.

- Inherently rigid structures

Inherently rigid structures in the backbone of the polymer molecule reduce the flexibility which produces a higher T_g value.

In summary T_g is a function of the rotational freedom and any restriction to rotation causes the value to increase. A single T_g value is exhibited for a random copolymer having amorphous morphology. The exact value is dependent upon the relative proportions of the respective monomers in the copolymer. Two very compatible

monomers should show one T_g value and it can be calculated from either of the following equations:

$$(T_g)_{AB} = (T_g)_A f_A + (T_g)_B f_B \quad (1.2)$$

$(T_g)_{AB}$ = Glass transition temperature of the copolymer

$(T_g)_A$ = Glass transition temperature of monomer A

$(T_g)_B$ = Glass transition temperature of monomer B

f_A = Volume fraction of monomer A

f_B = Volume fraction of monomer B

or

$$1/T_g = M_A/(T_g)_A + M_B/(T_g)_B \quad (1.3)$$

M_A = Mass fraction of monomer A

M_B = Mass fraction of monomer B

The latter equation is used to calculate approximate values for a random copolymer using mass fractions (equation 1.3). Polyblends comprising of incompatible polymers give a two phase structure and two T_gs are shown, one for each phase. The T_gs will correspond closely to their respective homopolymer values.

1.2.4 Crosslinking

The chemical bonds that occur between macromolecules are known as crosslinks. The mechanical and physical properties are influenced by the density of this linkage. Thermoplastics are uncrosslinked polymers which flow at high temperatures. By contrast, crosslinked polymers cannot melt due to the constraints on the molecular motion, introduced by this bond. At temperatures necessary to achieve the flow of thermoplastics, the polymers undergo irreversible degradation. Dissolution behaviour exhibited by uncrosslinked and cross linked polymers differ. They are dependent upon the nature and extent of the interchain covalent bonds. Polymers without this linkage dissolve if an adequate polymer-solvent compatibility is achieved. In contrast, polymers containing this linkage will not dissolve if the solvation of chain segments cannot overcome the effect of the covalent bonds between the macromolecules. The crosslink density of a polymer

controls the amount of solvent suspended within its matrix. The swelling is reversible in lightly crosslinked polymers and upon the removal of the solvent it may return to its original size. Polymers that are lightly crosslinked have the tendency to become soft and flexible, particularly above their glass transition temperature. A dense three dimensional network of covalent bonds is achieved by heavily crosslinking a polymer, producing a very brittle material. An increase in the number of covalent bonds reduces the freedom of motion by the individual segments of the molecules. Stress cannot be taken up by the structure and causes catastrophic failure at a given load with minimal deformation.

Difunctional or multifunctional monomers act as crosslinking agents, forming links between oligomers and other reactive molecules. This provides the polymer with increased elastic response, higher stiffness and a lower value of creep, compared to a non crosslinked polymer (Stevens M.P, 1990).

1.3 Preparation of Hydrogels

The method used to prepare hydrogels from hydrophilic monomers is free radical polymerisation (Rosiak et al., 1999, Ward J.H et al., 2001). This common technique involves the polymerisation of a water soluble monomer functionalised with a radically polymerisable group. An appropriate difunctional crosslinking agent, a low concentration of initiator and water may also be included at this stage. This is preferred for the preparation of interpenetrating network hydrogels (IPNs). These gels are networks, containing two polymeric systems each one with its own crosslinked system.

The chemistry of a typical free radical polymerisation involves three main steps; initiation, propagation and termination. A crosslinked polymer is formed when a difunctional monomer is added. The initiation step involves the formation of free radicals. An effective initiator readily undergoes homolytic fission when subjected to heat, electromagnetic radiation or chemical reactions. These radicals have greater reactivity than the monomer radicals. A typical radical producing reaction involves the homolytic scission of a single bond which results in the formation of free radicals, occurring at 50 – 100°C. The application of heat can effect the homolysis of certain compounds, particularly those containing peroxide (-O-O-) and azo (-N=N-) linkages. Figure 1.3

shows compounds containing these linkages and the formation of corresponding free radicals (Young R.J. et al, 1991, Cowie J.M.G., 1991).

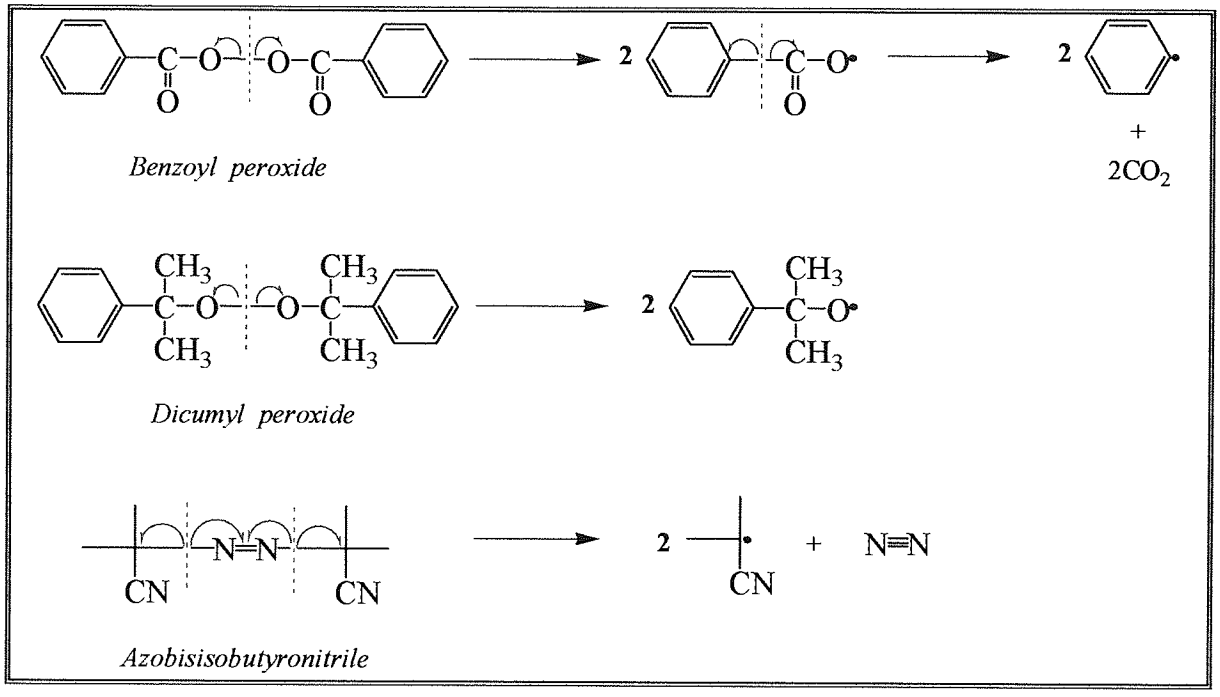


Figure 1.3 Compounds undergoing thermolysis resulting in the production of free radicals

Redox reactions involve the generation of free radicals by a one electron transfer reaction. This is particularly useful in the initiation of low temperature polymer and emulsion polymerisations. The reaction between an iron (2+) ion and hydrogen peroxide, in solution, produces hydroxyl radicals (equation 1.4).

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^- + OH^{\cdot} \qquad (1.4)$$

The hydrogen peroxide can be replaced with an alkyl hydroperoxide. A similar reaction is observed when cerium (4+) oxidizes an alcohol (equation 1.5).

$$RCH_2OH + Ce^{4+} \rightarrow Ce^{3+} + H^+ + RC(OH)H^{\cdot} \qquad (1.5)$$

Persulphates are useful in emulsion polymerisation, where decomposition takes place in the aqueous phase (equation 1.6). The radical diffuses into droplets of hydrophobic monomer.

$$S_2O_8^{2-} \rightarrow 2SO4^{\cdot-} \qquad (1.6)$$

Propagation is the addition of monomer units to the primary radicals, via a kinetic chain mechanism, which produces growth of the polymer chain. Termination occurs when two free radicals react with one another, halting the growth of the kinetic chain. Polymerisation can be achieved in bulk or in solution, both methods having advantages and disadvantages. A bulk polymerisation is often referred to as a neat polymerisation and involves a fast monomer conversion occurring over a few minutes. The main advantage is that no solvent removal from the polymer is required which conserves time and labour. This type of polymerisation was used for the production of sheet hydrogels. Solution polymerisation is advantageous if a large quantity of hydrogel is required.

The free radical addition of two different monomers to one another is known as copolymerisation. Problems arise when the reactivity of the monomers are not similar. The ability to produce polymers containing long sequences of two or more different monomers (block and graft) has led to new products with unique and valuable properties. The mechanism is analogous to that of homopolymerisation. However, the reactivities of monomers vary considerably from one another. Two monomers M_1 and M_2 can undergo either self-propagation where M_1 reacts with $M_1\bullet$ or M_2 reacts with $M_2\bullet$ or cross-propagation when $M_1\bullet$ reacts with M_2 or $M_2\bullet$ reacts with M_1 (Billmeyer F.W. Jr, Cowie J.M.G., 1991, 1984, Flory P.J., 1953, Young R.J. et al, 1991).

Propagation Reaction	**Rate**	
$M_1\bullet + M_1 \rightarrow M_1\bullet$	$k_{11}[M_1\bullet]\,[M_1]$	(1.7)
$M_2\bullet + M_2 \rightarrow M_2\bullet$	$k_{22}[M_2\bullet]\,[M_2]$	(1.8)
$M_2\bullet + M_1 \rightarrow M_1\bullet$	$k_{21}[M_2\bullet]\,[M_1]$	(1.9)
$M_1\bullet + M_2 \rightarrow M_2\bullet$	$k_{12}[M_1\bullet]\,[M_2]$	(1.10)

Under steady-state conditions, assuming that the radical reactivity is independent of chain length and depends only on the nature of the terminal unit, the rate of addition of $M_1\bullet$ to M_2 will equal the rate of addition of $M_2\bullet$ to M_1

$$k_{12}[M_1\bullet]\,[M_2] = k_{21}[M_2\bullet]\,[M_1] \qquad (1.11)$$

The rate of consumption of M_1 and M_2 from the initial reaction mixture is:

$$-d[M_1]/dt = k_{11}[M_1\bullet]\,[M_1] + k_{21}[M_2\bullet]\,[M_1] \qquad (1.12)$$

$$-d[M_2]/dt = k_{22}[M_2\bullet]\,[M_2] + k_{12}[M_1\bullet]\,[M_2] \qquad (1.13)$$

The ratio of the two rates is obtained by combining equations (1.12) & (1.13) together

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]}{[M_2]} \cdot \frac{k_{11}[M_1\bullet] + k_{21}[M_2\bullet]}{k_{22}[M_2\bullet] + k_{12}[M_1\bullet]} \qquad (1.14)$$

Defining r_1 and r_2 by the combination of equation (1.14) with the steady-state expression (1.11) gives:

$$\frac{k_{11}}{k_{12}} = r_1 \qquad (1.15)$$

$$\frac{k_{22}}{k_{21}} = r_2 \qquad (1.16)$$

and the copolymer equation can be derived

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]}{[M_2]} \cdot \frac{r_1[M_1] + [M_2]}{[M_1] + r_2[M_2]} \qquad (1.17)$$

$\frac{d[M_1]}{d[M_2]}$ = molar ratio of the two monomers in the copolymer

$[M_1]$ = initial molar concentration of monomer 1

$[M_2]$ = initial molar concentration of monomer 2

r_1 = reactivity ratio of monomer 1

r_2 = reactivity ratio of monomer 2

If $r_1 > 1$, M_1 tends to self propagate. However, if $r_1 < 1$, copolymerisation is preferred. The composition of the copolymer is independent of the overall polymerisation rate and initiator concentration. In most cases the reactivity ratios are unaffected by the

presence of chain transfer agents, inhibitors or solvents. If $r_1 = r_2 = 1$, the monomers will exhibit no preference for homopolymerisation or copolymerisation resulting in a truly random copolymer. This is an ideal situation. However if $r_1 = r_2 = 0$, neither monomers exhibit a tendency to homopolymerise forming a truly alternating copolymer. A simplified process to determine reactivity ratios has been developed. The ratios are expressed in terms of constants, characteristic of each monomer but independent of comonomer. This relationship is known as the Alfrey-Price equation (Young R.J. et al, 1991, Cowie J.M.G., 1991).

An expression for the rate constant of the cross-propagation can be derived as

$$k_{12} = P_1 Q_2 \exp(- e_1 e_2) \qquad (1.18)$$

P_1 relates to the radical $M_1\bullet$ and Q_2 relates to the M_2 monomer. e_1 and e_2 are proportional to the electrostatic interaction of the permanent charges on the substituents in polarising the double bond.

$$r_1 = \frac{Q_1}{Q_2} \exp[-e_1(e_1-e_2)] \qquad (1.19)$$

$$r_2 = \frac{Q_2}{Q_1} \exp[-e_2(e_2-e_1)] \qquad (1.20)$$

$$r_1 r_2 = \exp[-(e_1-e_2)^2] \qquad (1.21)$$

Q is a measure of the resonance stabilisation. For Cl and OR groups, $Q > 0.5$ and for an alkyl $Q < 0.1$. The polarity of the monomer is given the symbol e.

1.4 Biomedical Applications of Hydrogels

Hydrogels can be synthesised for a wide range of applications. Adjusting the method of preparation and composition affects the level of swell or mechanical strength (Dumitriu S., 2002).

1.4.1 Contact Lenses

Hydrogels are used for a range of applications for example as soft contact lenses (figure 1.4). Atmospheric oxygen dissolves in water and is transported by diffusion to the cornea. The first soft contact lenses were synthetically composed of poly HEMA with a water content of 38 %. Further investigation led to the discovery of a terpolymer gel HEMA – NVP – 4-t-butyl-2-hydroxycyclohexyl methacrylate with an equilibrium water content of 66 % ((Nicholson J.W., 2002).

The integral part of most cataract operations is the substitution of the crystalline lens for a transparent intraocular lens (figure 1.5). Foldable lenses composed of hydrophilic monomers (poly HEMA or copolymers of HEMA & MMA) were specifically designed to accommodate the small incision procedure used to replace the lens. Polymeric materials were compatible with the eye and produced a low level anti-inflammatory response (Dumitriu S., 2002).

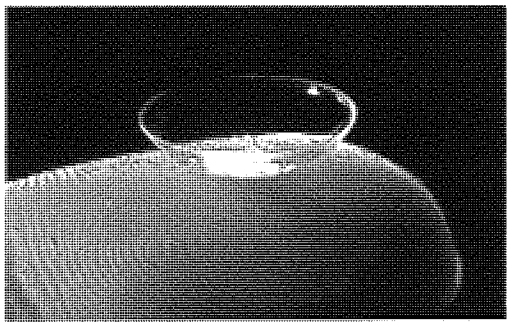


Figure 1.4 Contact lens

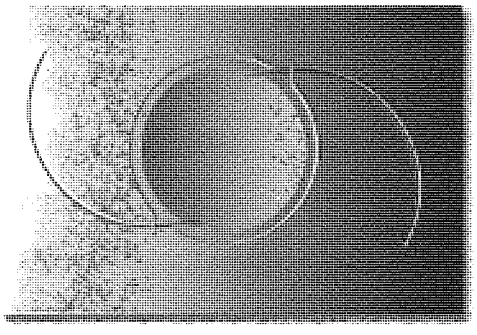


Figure 1.5 Intraocular lens

1.4.2 Tissue Prosthesis and Tissue Regeneration

Millions of people suffer from degenerative tissue joints. Hydrogels can be used to replace articular cartilage or tissue. Model systems enable the parameters controlling the biomechanical properties of articular cartilage to be simulated (Dumitriu S., 2002). A substantial amount of interest has been shown in the application of hydrogels as a tissue cell regenerator for the central nervous system (CNS).

1.4.3 Lubricants

Biomaterial surfaces lubricated with hydrogels, for example latex gloves, catheters and drainage tubes provide a lubricous coating. This enables the ease of use, when in contact with hydrophilic species (Dumitriu S., 2002).

1.4.4 Dressings

Hydrogels can be used for ulcerous or wound coverings. They act as barriers, preventing infection and moisten wounds, which promotes the healing process. Dressings absorb secretions and extrudate without adhering to the wound. Minimal trauma occurs when these dressings are removed (Dumitriu S., 2002).

1.4.5 Drug Delivery Systems

These drug delivery devices provide an alternative method to administer actives across the skin barrier. Gastrointestinal absorption is the traditional route for orally administered drugs. Patches contain a lower concentration compared to the oral dose. If any adverse symptoms begin to develop the gel can be removed, halting any further release (Tan H.S., et al, 1999). Figure 1.6 shows the various configurations of pressure sensitive adhesives used to administer actives. The adhesive layer enables skin adhesion, stores actives and controls the rate of delivery. The reservoir gel contains a rate controlling layer which enables the release of a desired quantity, whereas the monolithic configuration has an adhesive polymer matrix to control the rate of release. An active within the polymer matrix is the simplest form of a drug-in-adhesive gel. The components used within the

gel play a major role in the rate of release and can be modified by using different types of monomer.

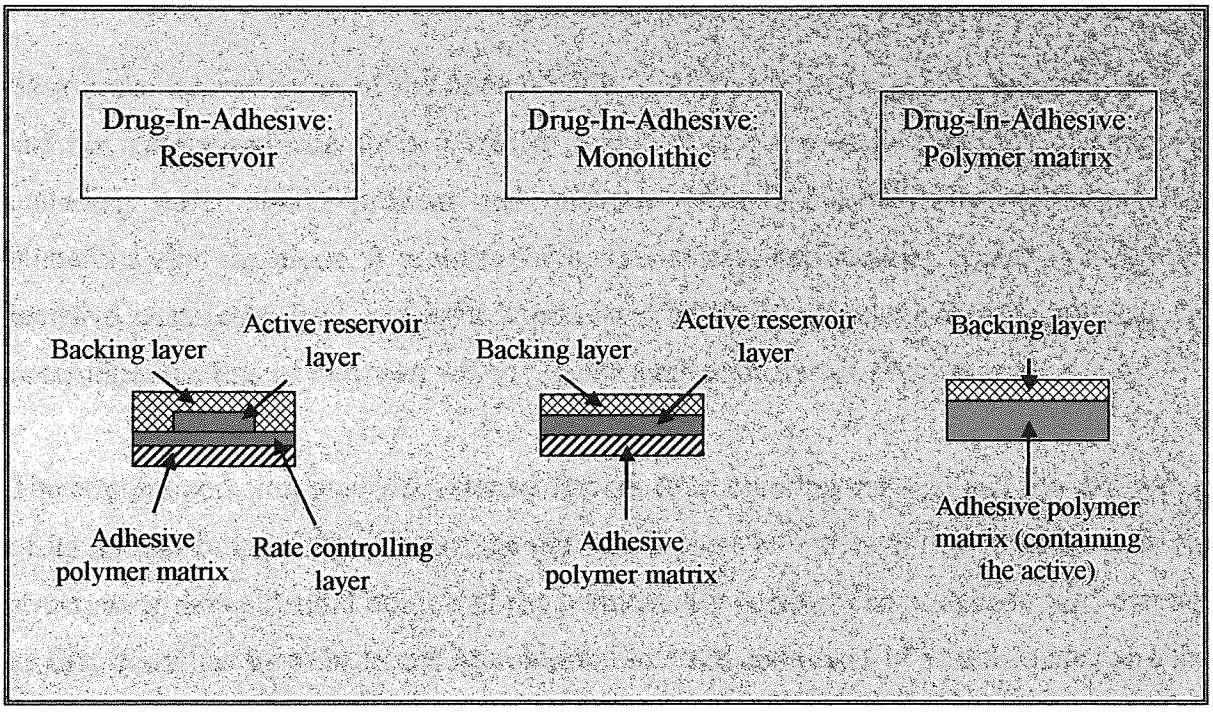


Figure 1.6 Classification of dermal delivery devices

1.5 Microanatomy of the skin

1.5.1 Introduction

Skin is the largest organ of the human body. It accounts for up to 16% of body weight and has an approximate surface area of $1.8m^2$. It is comprised of various components including water, lipids, proteins and minerals. Skin is metabolically active and has numerous vital functions. It protects the body's system and internal organs from injury, invasive chemicals, heat and light exposure. The body adapts to climatic changes by controlling the loss of moisture which regulates the temperature (Peppas et al., 2004).

The stratum corneum prevents external factors from entering the skin and the disruption of its normal functioning. An average pH of 5.5 plays an essential role in the formation, structure of the epidermal lipids and the permeability barrier. The protective acid mantle, as first described by Schade and Marchionini in 1928 comprises of sebum, sweat and the stratum corneum layer (including the intercellular lipid) (Peppas N.A, 1987). The various components that contribute to the acidic nature of the skin are:

- free fatty acids from sebum
- lactic acid and various amino acids in the sweat
- amino acids and 2-pyrrolidine-5- carboxylic acid from the stratum corneum layer.

An acidic environment is required for the:

- formation of the lipid bilayer membrane
- restoration of the stratum corneum layer following chemical or mechanical damage
- activation of the enzymes which synthesise important epidermal lipids.

1.5.2 Structural Layers of Skin

Skin is composed of three main structural layers (figure 1.7): the epidermis, the dermis and the hypodermis (Freinkel R., 2001, Gawkrodger D.J., 2000, Loden M. et al, 2000).

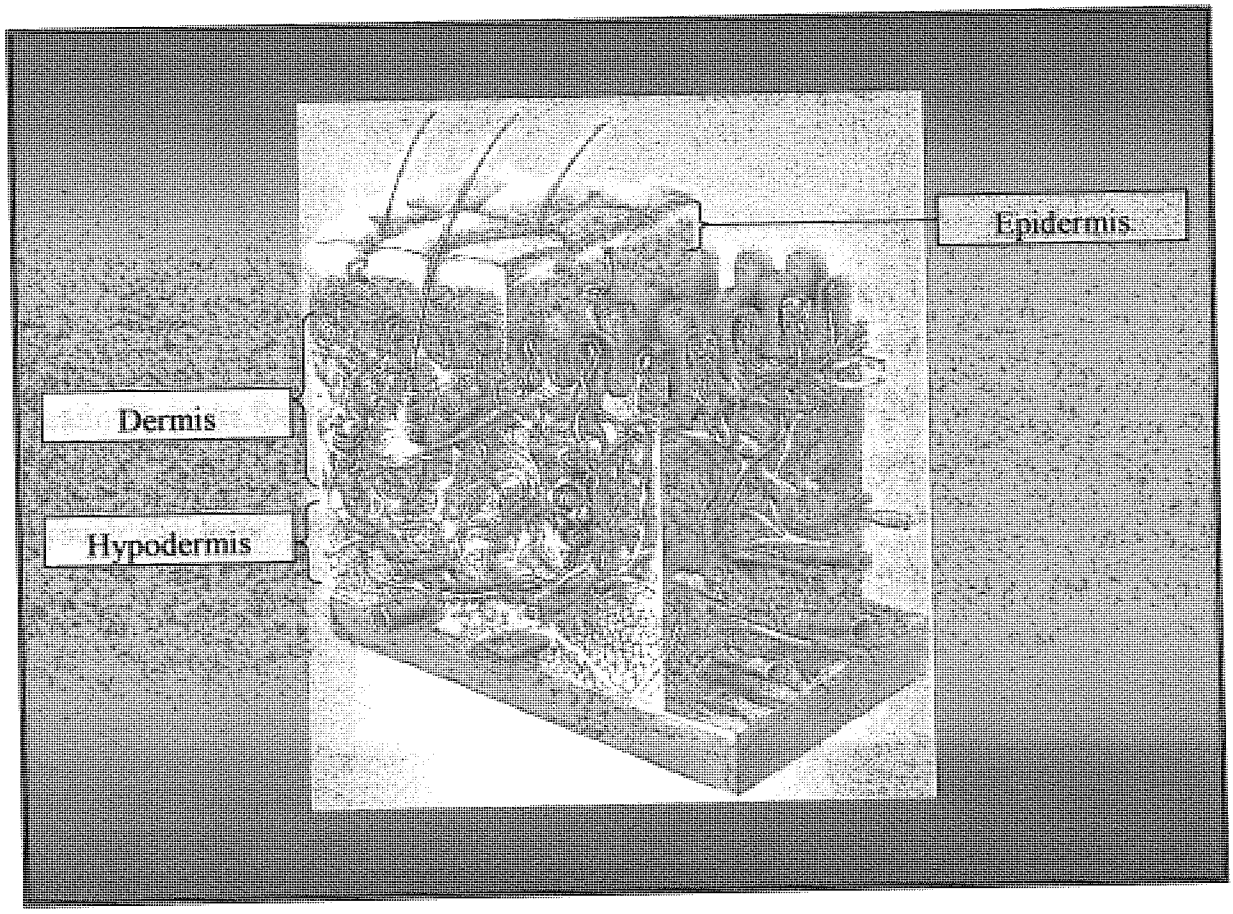


Figure 1.7 Structure of the human skin

1.5.2.1 Epidermis

The epidermis serves as a protective barrier and contains no blood vessels. Nourishment is received by diffusion from the dermis (Gawkrodger D.J., 2000, Loden M. et al, 2000). The approximate thickness is 0.1mm and on the palms and soles it is 0.8 to 1.4mm. Keratinocytes are specialised cells found within the epidermis and they produce the protein keratin. Its maturation occurs within four layers of the epidermis:

- *Basal cell layer (stratum basale)*

In this layer the stem cells produce corneocytes which divide by the process of mitosis, producing two daughter cells. Desmosomes are complex but are vital for cell adhesion and transport. Cells adjacent to the dermis are attached via the hemidesmosomes. 5-10% of the basal cell population is made up of melanocytes, which are transferred after synthesis to neighbouring keratinocytes.

- *Prickle cell layer (stratum spinosum)*

Daughter cells produced by cell division move away from the basal layer, migrating upwards forming a layer of polyhedral cells, interconnected by desmosomes. Bundles of keratin fibres are found between the desmosomes. The nuclei of these cells strengthen the framework. Continual cell division takes place resulting in an upward movement of cells through the layer. During the maturation process of spinous cells, they accumulate specialised organelles (e.g. membrane-coating granules, lamellar bodies or granular bodies). Dendritic, immunologically active Langerhans cells are found within this layer.

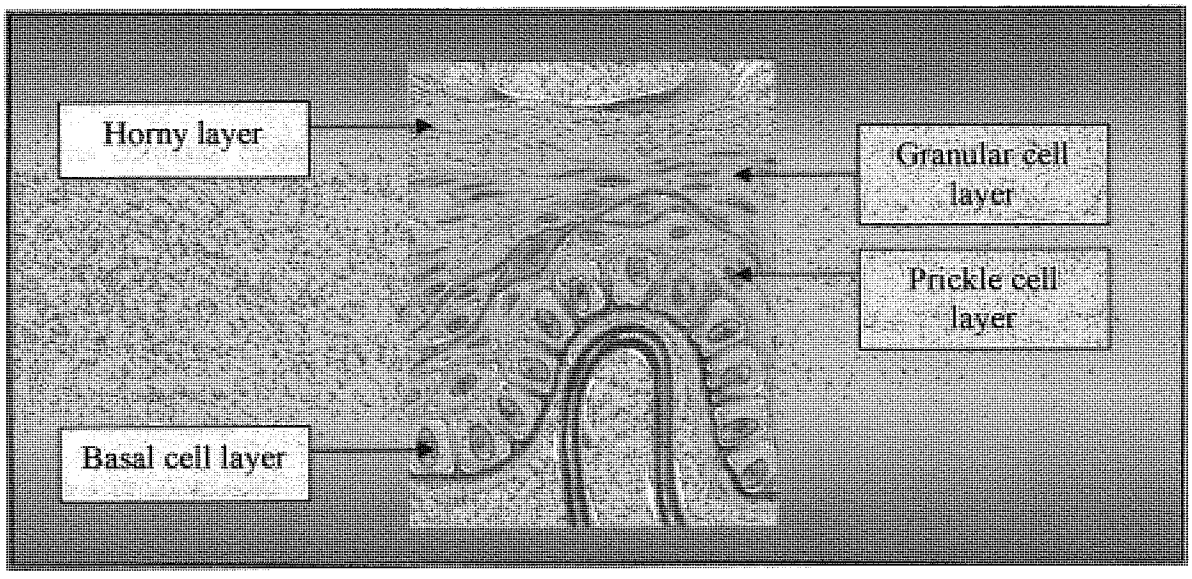


Figure 1.8 Diagram of the epidermis

- *Granular cell layer* (*stratum granulosum*)

There are typically two to four layers of cells within this layer. They eventually become flattened and lose their nuclei. The deposits of keratohyalin in the cytoplasm and membrane coated granules are responsible for the granular appearances of the cells. They expel their lipid contents into extracellular spaces. The upward movement of granular cells towards the skin surface produces an increase of lamellar granules.

- *Horny layer* (*stratum corneum*)

Keratinocyte maturation occurs in the horny layer. Corneocytes are polyhedral, cornified cells which form overlapping sheets. The cell envelope broadens and the cytoplasm is replaced by keratin tonofibrils. Cells are stuck together by a lipoidal glue, which is partly derived from membrane coating granules. This layer is 10-20 μm in thickness.

1.5.2.2 Dermis

This layer is 1-2mm in thickness and is situated immediately below the epidermis. It is composed of a tough, supportive, connective tissue matrix and contains specialised structures (Gawkrodger D.J., 2000, Loden M. et al, 2000). The thin upper layer known as the papillary dermis is composed of loose inter woven collagen. Deep, thick reticular dermis contains coarser and horizontally running bundles of collagen. The dermis is composed of collagen fibres which impart strength and toughness to the structure. Elasticity of the skin is provided by the loosely arranged elastin fibres, in all directions of the dermis. Dermal dendrocytes, fibroblasts, lymphocytes and macrophages are contained within this layer.

1.5.2.3 Hypodermis

This is the thickest and innermost layer of the skin (1-2mm thickness). It consists of loose connective tissue and fat attached to the dermis by collagen and elastin fibres (Gawkrodger D.J., 2000, Loden M. et al, 2000). The hypodermis is an energy reserve. Adipocyte cells accumulate and store fat. A reduction in energy providing substances trigger the release of fat from these cells which is transformed into energy. The

hypodermis is distributed over the entire body, providing thermoregulation and protection for vital inner organs.

1.5.3 Melanocytes

These dendritic cells are found in the basal layer of the epidermis. Their main function is the production of the pigment melanin, which gives skin its colour (Alfons T.L, 2003, Bolognia J.L. et al.). Tyrosine is the building block of melanin found within melanocytes. It takes two forms:

- eumelanin – more common and gives a black-brown colour
- phaeomelanin – less common and gives a yellow or red colour.

Figure 1.10 shows the biosynthetic pathway of melanin production, a high molecular weight polymer with a complex structure. Eumelanin is formed via oxidative phosphorylation. Melanonsomes (figure 1.9) are membrane bound organelles. They are packed with granules of melanin which are transferred by phagocytosis to adjacent keratinocytes. Each melanocyte supplies melanin to thirty five keratinocytes.

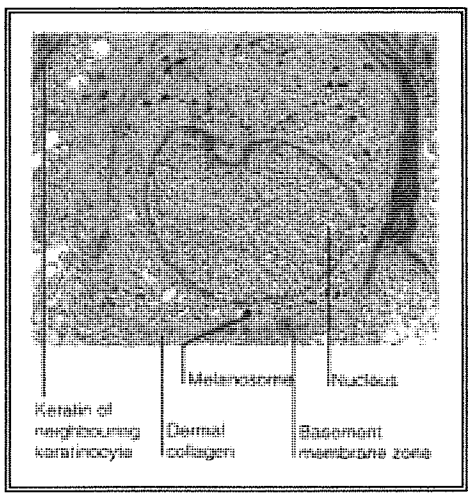


Figure 1.9 A electronmicrograph of a melanocyte

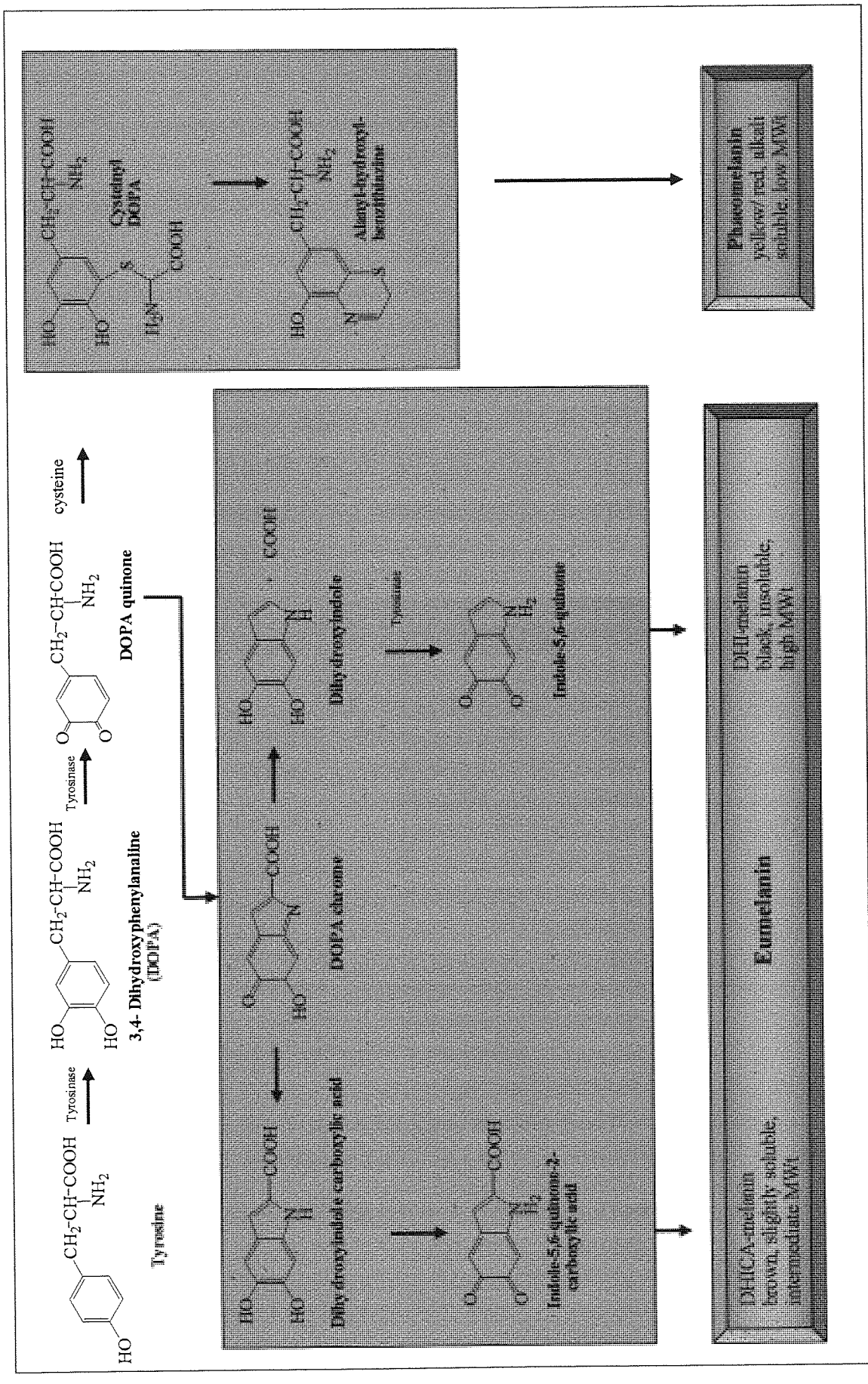


Figure 1.10 Biosynthesis of melanin in the human body

The melanin granules form a protective cap over the outer part of the keratinocyte nuclei. They are distributed throughout the stratum corneum forming a UV absorbtion blanket. This reduces the amount of radiation penetrating the skin. Hydroquinone is known to cause depigmentation. Skin containing eumelanin shows visible signs of this effect compared to one containing phaeomelanin. It is essential that monomers containing low levels of inhibitor are used to synthesise gels.

1.5.4 Composition of Skin Lipids

Lipid synthesis occurs during the differentiation of epidermal keratinocytes (Freinkel R., 2001, Gawkrodger D.J., 2000, Loden M. et al, 2000, Eucerin). They are imperative to the correct functioning of the skin barrier. Membranes residing in the living epidermis predominantly consist of phospholipids. Table 1.1 shows the composition of sebaceous lipids and epidermal lipids. The former type of lipid is produced by the sebaceous glands. Fatty acid esters, cholesterol and ceramides are found within the horny layer. Wax esters and squalene are predominantly found within sebum.

Component	**Sebaceous lipids (%)**	**Epidermal lipids (%)**
Glyceride/Free Fatty Acids	58	65
Wax esters	26	0
Squalene	12	0
Cholesterol esters	3	15
Cholesterol	1	20

Table 1.1 Sebum and epidermal lipid composition

Epidermal lipids are produced in the Golgi apparatus, within the keratinocytes. They are stored as bilayers in the Odland bodies (figure 1.11, No.1). The lipid bilayer membranes are expelled into the intercellular space by exocytosis (figure 1.11, No. 2) in the upper

layer of the granular layer. Enzymes within skin convert polar glycolipids, phospholipids and sterol esters to non-polar lipids, ceramides and free fatty acids. This occurs during the maturation process and provides the important functional semipermeable corneocyte lipid bilayer (figure 1.11, No. 4).

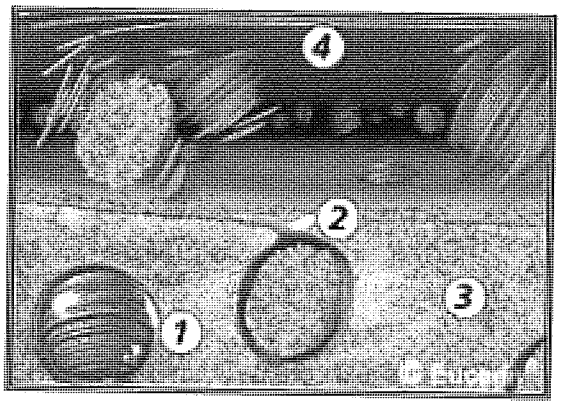


Figure 1.11 Synthesis of lipids

No. 1 Odland bodies
No. 2 Exocytosis
No. 3 Cells of the stratum granulosum
No. 4 Bilayer lipid membrane

The lipid layer assists in the reduction of transepidermal water loss from the skin. Lipids undergo peroxidation in the presence of sunlight, particularly UV light and air. If lipids lose their barrier ability, gaps appear in the skin matrix, increasing transepidermal water loss (TEWL).

1.5.5 Natural Moisturising Factor

In the 1950's Irwin Blank demonstrated that dry, flaky skin contributed to the low moisture content (Loden M., 2000). The stratum corneum is a thin, inert, water retaining barrier, produced when the epidermis undergoes the process of maturation. The structure is heterogeneous and has been likened to a brick wall, with corneocytes, anucleated non viable cells (bricks), embedded in a continuous matrix of specialised intercellular lipids (mortar).

A corneocyte is a highly insoluble protein complex which consists primarily of a keratin macrofibrillar matrix, stabilised through inter- and intrakeratin chain disulfide bonds. The cornified cell envelope encapsulates it within the protein shell, protein interactions impart great strength.

The stratum corneum must remain hydrated to maintain its flexibility and integrity. Healthy skin tissue contains more than 10% water. The water balance within the stratum corneum is vital to the functioning of this organ. An absence can result in the structure becoming brittle, cracked and rigid. Two major biophysical mechanisms preserve the integrity of the skin. They interact together maintaining hydration and flexibility:

- *intercellular lamellar lipids* provide an effective barrier to the passage of water through the tissue
- *NMF* is a complex mixture of low molecular weight, water soluble compounds which are present within the corneocytes.

Tissue hydration is maintained by the collective NMFs. They bind to water and react against the desiccating action of the environment. The highly structured intercellular lipid lamellae has another function, preventing the highly water soluble NMF from leaching out of the surface layers of the skin. This barrier is prone to damage from external forces. Breakdown of this layer causes excessive water loss, leading to dry skin. Desiccation of tissue causes a decline in hydrolytic enzyme activity, leading to ineffective corneodesmosomal degradation and skin scaling.

1.5.6 Role of the NMF in the stratum corneum

The NMF consists primarily of amino acids and their derivatives, 2-pyrrolidone-5-carboxylic acid (PCA), urocanic acid (UCA), lactic acid, urea, citrate and sugars (table 1.2).

Chemical Component	%
Free amino acids	40.0
Pyrrolidone carboxylic acid	12.0
Lactate	12.0
Sugars, organic acids, peptides, unidentified materials	8.5
Urea	7.0
Chloride	6.0
Sodium	5.0
Potassium	4.0
Ammonia, uric acid, glucosamine creatine	1.5
Calcium	1.5
Magnesium	1.5
Phosphate	0.5
Citrate, formate	0.5

Table 1.2 Chemical composition of the NMF

The dry weight of the stratum corneum is composed of 20-30% of NMF. PCA and lactic acid salts act as highly efficient humectants by absorbing atmospheric water. The quantity of NMF in the stratum corneum dictates how much water can be stored. Stratum corneum can only absorb significant amounts of water at 100% humidity, in the absence of NMF. This situation seldom occurs (Loden M., 2000, Freinkel R., 2001).

Fox et al investigated the humectancy capability of sodium lactate at 60% relative humidity (RH). A 60% increase in the water content was observed. Under the same conditions glycerol provides a 38% increase. Laden and Spritzer investigated the composition of the NMF. They concluded that amino acids are relatively non hygroscopic at skin pH and that PCA contributes significantly to the water binding capacity within the stratum corneum.

The stratum corneum is plasticised by water, preventing it from flaking or cracking under mechanical stress. When the RH is reduced, water provides a transient effect. The topical application of lactic acid showed that a long term plasticisation of the stratum corneum was achieved. The precise mechanisms by which the NMF components influence the stratum corneum functionality have been studied. The interaction between the keratin and NMF is accompanied by a decrease in the mobility of water. The intermolecular forces between the keratin fibres decrease and the elastic behaviour increases.

NMFs have a dual role; they maintain free water in the stratum corneum and facilitate biochemical reactions. The optimal functioning of the stratum corneum is coordinated by the activity of specific proteases. These hydrolytic processes only function in the presence of water which is effectively achieved by the water retaining the capacity of the NMF.

1.5.7 The Origin of the NMF

In the early 1980's Scott and co-workers investigated the source of amino acids and their derivatives within the stratum corneum. These studies led to the conclusion that NMF amino acid components were derived from a single, high molecular weight, rich protein called histidine. This represented the major component of the F-type keratohyalin granules. During the transition of mature granular cells into corneocytes, the protein was rapidly dephosphorylated. It underwent a selective proteolytic process to form low molecular weight species, within the stratum corneum.

PCA is derived by non enzymatic cyclisation of glutamine and UCA. The latter is a natural UV absorber formed by the action of the enzyme histidase on histidine (Loden M., 2000, Freinkel R., 2001).

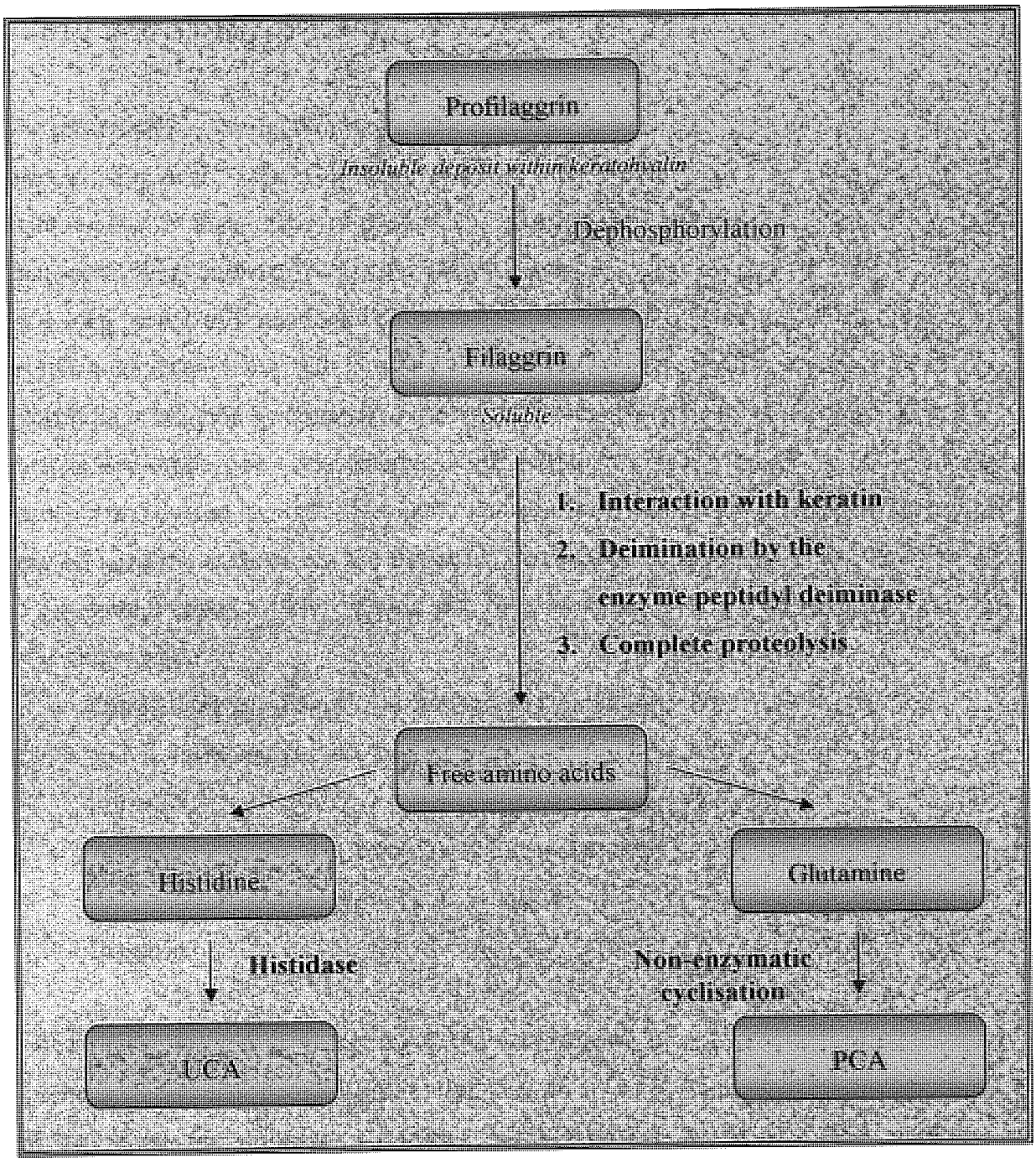


Figure 1.12 Schematic representation of profilaggrin catabolism during differential differentiation

1.5.8 Control of Filaggrin Hydrolysis

The proteolytic breakdown of filaggrin is initiated in the outermost layers of the stratum corneum (Freinkel R., 2001, Loden M., 2000). This process can be prevented if a humid environment is maintained. Experimental studies of isolated stratum corneum, at a relative humidity range of 70 to 95%, showed that hydrolysis occurred. Occlusion of skin for a long period of time blocks filaggrin hydrolysis. The corneocytes remain filled with protein and NMF level fall close to zero. These observations suggest that filaggrin hydrolysis is initiated by changes in the water activity within the stratum corneum itself.

The epidermis does not generate NMF within the viable layers or newly formed corneocytes, due to the risk of osmotic damage. Activation of the filaggrin protease is delayed until the corneocytes are flattened, strengthened and move out into the dry area of the stratum corneum. The osmotic effects of the NMF pool can be sustained when the following occurs:

- Synthesised profilaggrin is precipitated within the keratohyalin granule and it is insoluble. An osmotically inactive repository of the NMF is important
- A proteolytic resistant complex is formed due to the interaction between the keratin and filaggrin. This prevents premature proteolysis of the filaggrin.

A decrease in the moisture content of the skin triggers a natural biological mechanism. Corneocytes containing the filaggrin migrate in an upward direction and they begin to dry out activating the proteases to ensure NMF production. Initiation of this type of hydrolysis is independent of the age of the corneocyte and is ultimately dictated by the environmental humidity. During humid weather the proteolysis occurs almost at the outer surface and when the humidity is extremely low proteolysis is initiated deep within the tissue. So, all but the deepest layers contain NMF, required to prevent desiccation. The stratum corneum has a self moisturising mechanism which responds to the exposure of different climates.

1.5.9 NMF Levels and Dry Skin Conditions

A dermatological disorder arises if there is a failure in the production or processing of profilaggrin. This type of disorder is diagnosed as ichthyosis vulgaris. Histological studies have shown that the NMF content reaches close to zero. The absence of keratohyalin granules also result in the deficiency of NMF. The inability to produce and retain NMF within the stratum corneum is a significant factor which contributes to dry skin. Exposure of normal skin to a routine soap wash results in the reduction of NMF. In deeper layers of the skin the NMF binds to water maintaining an optimum level of hydration. Numerous characteristics for example the roughness, mild scaling, tightening and possible itching, can be used to identify dry skin. A lack of epidermal lipids results in the increase in the transepidermal water loss and will result in the skin drying out unless the problem is rectified (Loden M., 2000, Freinkel R., 2001).

1.5.10 Desquamation

Terminal keratinocyte differentiation is the process by which the stratum corneum is continuously formed. The rate of cell proliferation in the basal layer of the epidermis determines the rate of stratum corneum renewal. Desquamation is a normal process which occurs invisibly with the shedding of individual cells or small aggregates of cells. This produces a smooth appearance of the skins surface, associated with normal skin. This takes place every minute of every day and in total 30,000 – 40,000 dead skin cells are lost of the surface, approximately 4kg of cells every year. The turnover time of the stratum corneum is two to four weeks. The corneocytes are essentially termed as being 'dead' since they do not synthesise protein or produce cell surface structures. Disturbance in this process results in the accumulation of partially detached cells on the skin surface. Corneocyte cohesion must be eliminated for desquamation to continue. This is initiated by the keratinocytes within the viable parts of the epidermis. Stratum corneum chymotrypic enzyme (SCCE) is produced as an inactive precursor. It is converted to an active enzyme by proteolytic modification by trypsin-like enzymes (Loden M., 2000).

1.6 Aims of the Research

The main objective of this research is to develop tailor-made skin adhesives with the capability of releasing moisturising agents. 2-Acrylamido-2-methyl-1-propanesulfonic acid sodium salt (NaAMPS), an ionic monomer was used in numerous skin adhesive applications and this will be the essential starting point. Compositions containing this monomer need to be examined in order to determine the fundamental factors which affect the adhesive and mechanical properties.

Copolymers of NaAMPS will be investigated to determine if the cohesive properties of the gel can be enhanced, enabling it to be viable for a range of applications including an ostomy adhesive. This allows the attachment of a device which collects extrudate from a surgically made opening in the abdomen. Poly NaAMPS has a high affinity for water and gels with the ability to absorb fluids without losing their structural integrity could be examined.

The gels must adhere to the skin and therefore it is essential to investigate which chemicals can enhance the adhesiveness of a hydrogel. The potential market for skin adhesives is vast and they need to be available to a wide range of consumers. Attachment to the different skin types must be considered including normal and in particular greasy skin. The technology used to synthesise skin adhesive hydrogels must be expanded and therefore two phase systems (hydrophilic and hydrophobic) will be examined.

The different types of technology should allow an array of actives to be incorporated to address the problem of inadequate hydration of skin. Active agents will be selected for their potential to increase hydration of the stratum corneum. Further studies need to be pursued to show if the actives can be released from the three dimensional polymer matrixes. It is essential that the release of actives increase the hydration levels and a suitable method of monitoring is necessary.

Chapter 2

Reagents and Methodology

2.1 Reagents

The reagents used in the experimental work are shown in the following table:

Reagent	Molecular Weight	Abbreviation	Supplier
Acrylic acid	72.06	AA	Aldrich
2-Acrylamido-2-methyl-1-propanesulfonic acid sodium salt	229.25	NaAMPS	First Water
4-Acryloylmorpholine	141.17	AMO	Aldrich
Acronal	N/A	None	BASF
2,2 Azobisisobutyronitrile	164.21	AIBN	Aldrich
Butyl acrylate	128.17	BA	Aldrich
D-Calcium Pantothenate	238.27	Pro Vit B5	Fisher
5',5'' dibromopyrogallol-sulfonephthalein	92.09	Bromopyrogallol red	Fisher
Diethyl ether	74.0	None	Fissons
N,N dimethyl acrylamide	99.13	N,N DMA	Aldrich
DM137	N/A	DM137	First Water

Reagent	Molecular Weight	Abbreviation	Supplier
Epoxidised soybean oil acrylate	Not stated	ESBA	Aldrich
Ethylene glycol	62.07	EG	Aldrich
Ethylene glycol dimethacrylate	198.22	EGDMA	Aldrich
Flexbond 150	N/A	Flexbond 150	First Water
Glycerol	92.09	G	First Water
2-Hydroxyethyl methacrylate	130.14	HEMA	Aldrich
1-Hydroxycyclohexyl phenyl ketone	204.27	Irgacure 184	Ciba
Jojoba oil	N/A	JJ oil	Fluka
Lactobionic acid	358.30	LBA	Fisher
Lauryl acrylate	240.38	LA	Aldrich
Methanol	32.04	None	Fissons
N,N methylene bis acrylamide	154.17	None	Aldrich
OXONE®monopersulfate compound	614.76	OXONE	Aldrich

Reagent	Molecular Weight	Abbreviation	Supplier
Polyethylene glycol (600) diacrylate	N/A	EbII	UCB
Polyethylene glycol myristyl tallow ether	~3000	PEG mte	Aldrich
Polyoxyethylene sorbitan monolaurate	~1228.0	Tween 20	Aldrich
Polyoxyethylene sorbitan monostearate	1311.7	Tween 60	Aldrich
Poly(propylene glycol)-block-poly(ethylene glycol)-block-poly(propylene glycol) Pluronic P65	Ave. 3400	P65	BASF
Poly(propylene glycol)-block-poly(ethylene glycol)-block-poly(propylene glycol) Pluronic F108	Ave.14600	F108	BASF
Polyquaternium 4	N/A	PQ4	ICI
Polyquaterium 10	N/A	PQ10	ICI
2-Pyrrolidone-5-carboxylic acid	129.11	PCA	Aldrich

Reagent	Molecular Weight	Abbreviation	Supplier
Stearyl acrylate	324.54	SA	Aldrich
Texicryl 13056WB	N/A	Tex13056	Scott Bader
N-Vinyl-2-pyrrolidone	111.1	NVP	BASF
Vitamin C	176.12	Vit C	Aldrich
Vitamin E	430.71	Vit E	Aldrich

Table 2.1 Reagents used in this study

2.2 Structures

2.2.1 Monomers

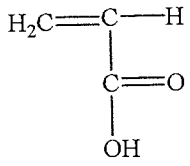
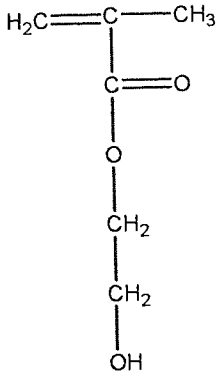
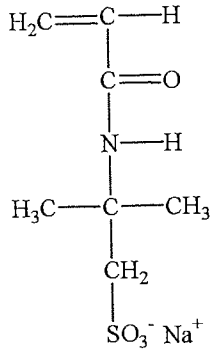
		
Acrylic acid	2-Hydroxyethyl methacrylate	2-Acrylamido-2-methyl-1-propanesulfonic acid sodium salt

Figure 2.1 Hydrophilic monomers

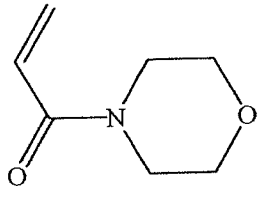
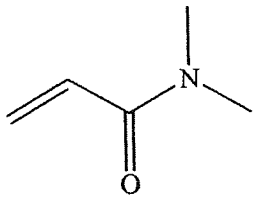
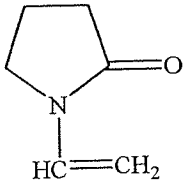
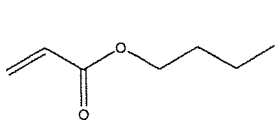
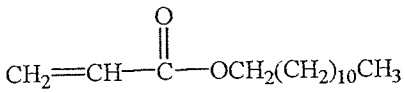
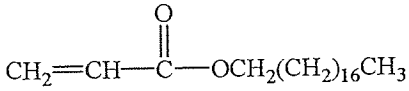
		
4-Acryloylmorpholine	N,N dimethyl acrylamide	N-vinyl-2-pyrrolidone

Figure 2.2 Solvent Bridging monomers

		
Butyl acrylate	Lauryl acrylate	Stearyl acrylate

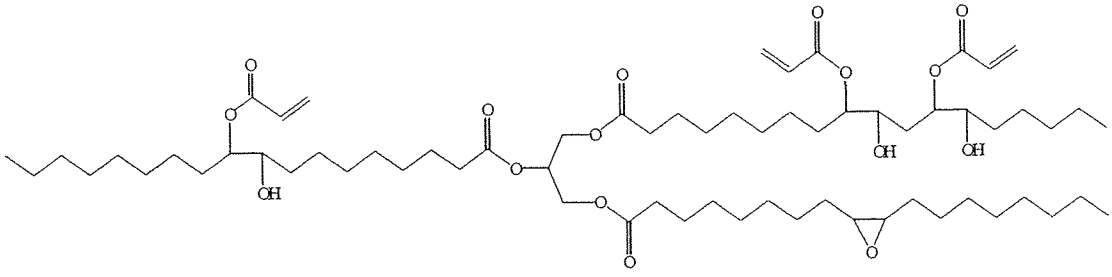

Epoxidized Soybean oil acrylate

Figure 2.3 Hydrophobic monomers

2.2.2 Active/Lipoidal agents

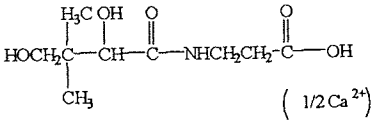
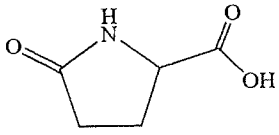
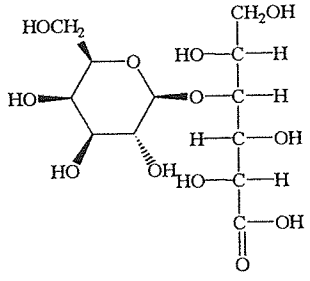
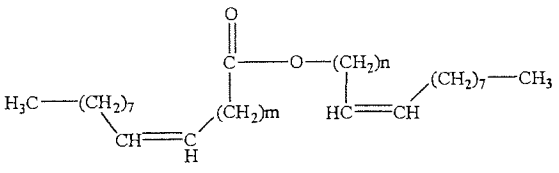
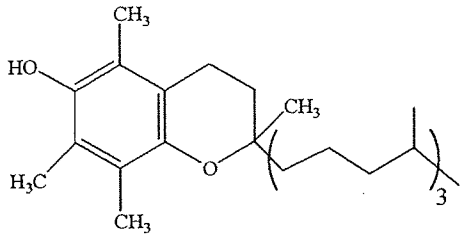
		
D-Calcium Pantothenate	2–Pyrrolidone-5-carboxylic acid	Lactobionic acid

Figure 2.4 Active agents



Jojoba oil



Vitamin E

Figure 2.5 Lipoidal agent

2.2.3 Humectants

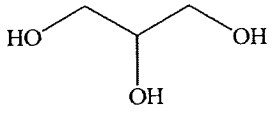
$HOCH_2CH_2OH$	
Ethylene glycol	Glycerol

Figure 2.6 Humectants

2.2.4 Crosslinkers

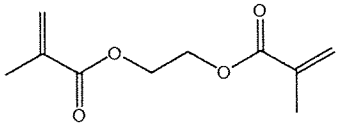
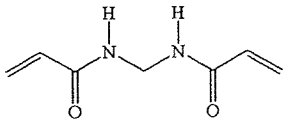
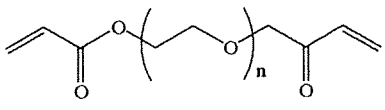
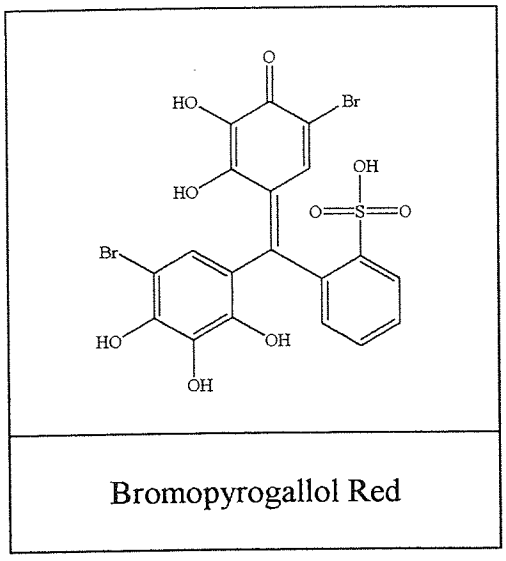
		
Ethylene glycol dimethacrylate	N,N methylene bis Acrylamide	PEG (400) diacrylate

Figure 2.7 Crosslinkers

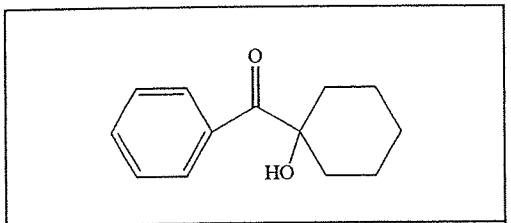
2.2.5 Organic dye



Bromopyrogallol Red

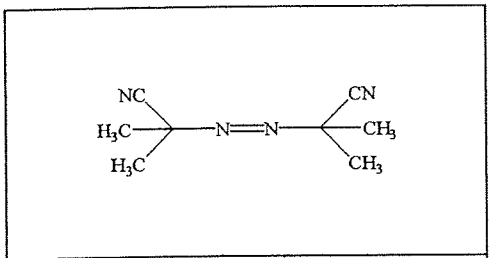
Figure 2.8 Organic dye

2.2.6 Initiators



Irgacure 184

Figure 2.9 Photoinitiator



2,2 azobisisobutrynitrile (AIBN)

Figure 2.10 Thermal Initiator

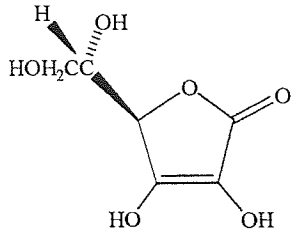
	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
Ascorbic acid	OXONE, monopersulfate compound

Figure 2.11 Redox Initiator Pair

2.2.7 Viscosity Modifiers

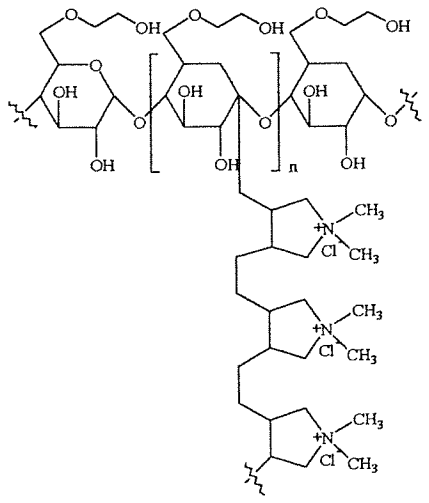
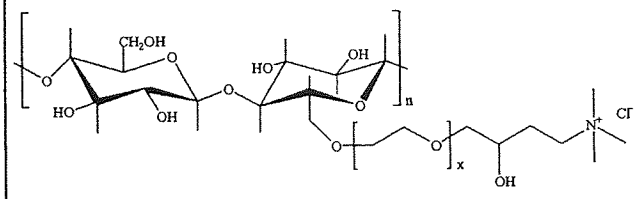
	
Polyquaterium 4	Polyquaterium 10

Figure 2.12 Viscosity modifiers

2.2.8 Surfactants

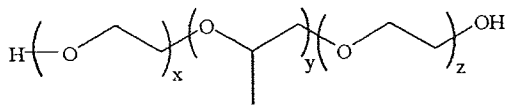
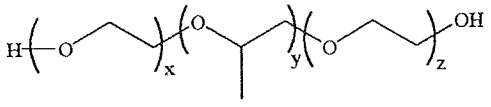
 Ave Mn 3400	 Ave Mn 14600
Pluronic P65	Pluronic F108

Figure 2.13 Block copolymer non ionic surfactants

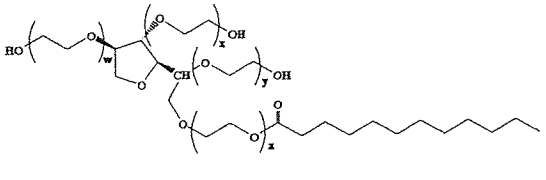
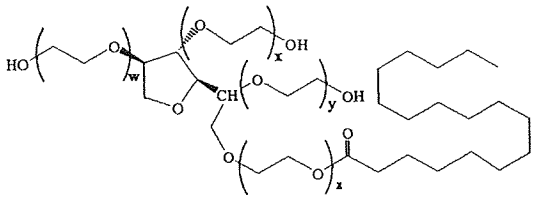
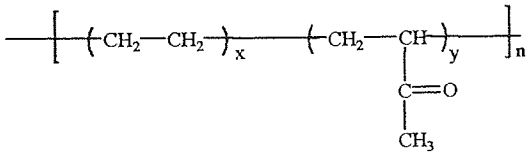
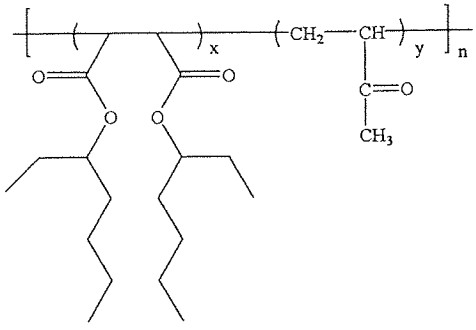
 W + X + Y + Z = 20	 W + X + Y + Z = 20
Tween 20	Tween 60

Figure 2.14 Non ionic Tween surfactants

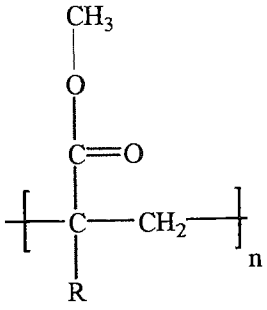
2.2.9 Pre formed commercial emulsions



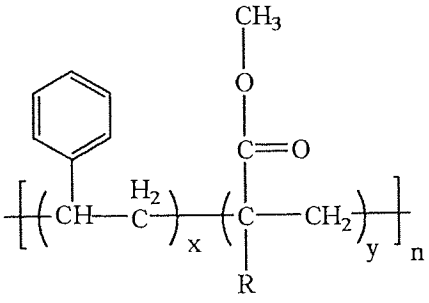
Poly(Ethylene-co-vinyl acetate)
DM137



Poly(Dioctyl maleate-co-vinyl acetate)
Flexbond 150



Poly Acrylic
Texicyl 13056 WB



Poly (Styrene –acrylic)
Acronal

Figure 2.15 Pre formed O/W emulsions

2.2.10 Solvents

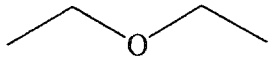
	CH_3OH
Diethyl ether	Methanol

Figure 2.16 Solvents

2.3 Procedures

2.3.1 Methods of Polymerisation

2.3.1.1 Thermally initiated polymerisation

Non adhesive hydrogels were synthesised using a formulation, consisting of 5g monomer (or a mixture of monomers), 1% w/w thermal initiator (e.g. AIBN) and 1% w/w crosslinker (e.g. methylene bisacrylamide). The pregel was sonicated before being placed into a prepared glass mould. Figure 2.17 illustrates the steps followed to prepare the glass mould, which held the pregel mixture. In step 1 two glass plates were covered with a sheet of melinex (polyethylene terephthalate), to reduce the risk of contamination which could potentially reduce or hinder the rate of polymerisation and two polyethylene (PE) gaskets placed in the central area of the mould, to ensure that any risk from contamination was minimal (step 3).

A G22 syringe needle was placed between the two polyethylene gaskets allowing the pregel mixture to be injected (step 4). The mould was sealed (step 5) by positioning spring clips as illustrated which allowed only the small internal cavity to be filled. The mould was kept in an upright (vertical) position during the injection process of the pregel, to reduce the amount of air entering and to ensure that the cavity was completely full. Upon removal of the syringe, two spring clips were placed on top of the mould (step 6). Polymerisation was initiated by placing the mould into a preheated oven set to 60°C, for 3 days. The gel was post cured for a further 3 hours, in a preheated oven set to 90°C (step 7). Removal of the gel, from the mould, took place after it had cooled to room temperature. Finally the gel was placed in distilled water to allow it to hydrate and to ensure the removal of any unreacted chemicals. The medium was changed daily, for five days, giving the gel ample time to reach equilibrium hydration.

Step 1. *Two identical glass plates and two sheets of melinex (PET) (10 x 15cm) were required to construct the mould.*

Step 2. *A melinex sheet was affixed to the glass plate with the aid of the spray mount. The same procedure was repeated for the other glass plate*

Melinex sheet attached to the glass plate by the using spray mount adhesive

Step 3. *Two PE gaskets measuring 10 x 15cm were cut as shown below. They were placed onto the melinex covered glass plate (MCG plate).*

Step 4. *The mould was assembled as shown in the diagram below. A G22 needle was placed between the two PE gaskets.*

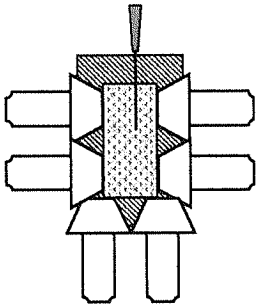
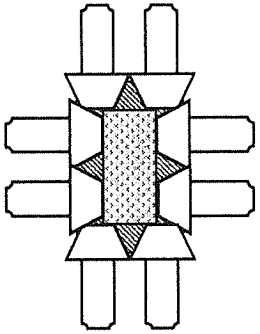
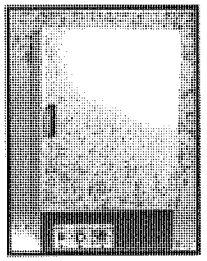
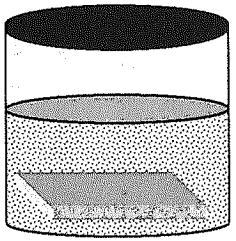
Step 5. *Spring clips were placed around the mould to hold the gaskets in position. The pregel was injected into the mould using a 5ml syringe.*	***Step 6.*** *The mould was sealed with the aid of spring clips which also held the gaskets into position as shown below.*
	
Step 7. *The mould was placed into a preheated oven set to 60°C for 3 days and then post cured at 90°C for 3 hours. After this time the gel was allowed to cool before being removed from the mould.*	***Step 8.*** *The gel was placed into H_2O to allow it to hydrate and to assist in the removal of residual monomers. The medium was changed daily for 5 days in total.*
	

Figure 2.17 Methodology used to synthesise fully hydrated non adhesive hydrogels

2.3.1.2 Redox initiated polymerisation

The reaction mechanism for redox polymerisation is similar to that of thermal polymerisation, with one significant difference. The initiation process involves the generation of free radicals via the net electron flow to and from a defined centre, during a chemical reaction. This type of initiating system reduces the time taken for polymerisation from days to minutes, compared to thermal polymerisation.

Stock solutions of the initiator pair were made up in separate vials, using 0.5g ascorbic acid in 10ml H_2O and 0.5g OXONE in 10ml H_2O and N_2 was passed through each stock solution. 3g of monomer (e.g. HEMA) and 0.05g crosslinker (e.g. ethylene glycol dimethacrylate) were placed in a small sample vial and mixed, using an IKA VIBREX VXR shaker for 10 minutes at 150 revs/min [solution A]. 1g of ethylene glycol and 0.5ml of the OXONE stock solution were placed in another small sample vial and mixed for 10 minutes, on the IKA VIBREX VXR shaker [solution B].

Solution B was added to solution A and then N_2 was passed through the solution mixture. 0.5ml of the ascorbic acid stock solution was added and mixed, for five seconds. The solution was injected into a pre-prepared glass mould, identical to those used in the thermal polymerisation process as shown in figure 2.17. The gel formed after five minutes but the mould was left intact for an hour, to ensure that adequate time had elapsed for polymerisation to be completed and that all of the free radicals had been consumed. The gel was removed from the mould and placed in distilled water. The medium was changed daily for five days before the gel could be used for further experiments.

2.3.1.3 UV initiated polymerisation

Partially hydrated skin adhesive hydrogels were prepared in the presence of an appropriate photoinitiator. In the presence of UV light this chemical dissociates to form free radicals. A typical formulation used to prepare skin adhesive hydrogels consists of 40% w/w unsaturated hydrophilic monomer (e.g. NaAMPS), 30% w/w glycerol and 30% w/w distilled H_20 (typically the total mass of these components add up to 100g). The chemicals were weighed or measured and subsequently transferred into a large glass bottle. This was placed onto the orbital shaker for 30 minutes, set at 200 revs/min, to ensure that a homogenous solution was obtained [Solution A].

3 parts photoinitiator (e.g. Irgacure 184) and 10 parts of crosslinker (e.g. Ebacryl II) were transferred into a small sample vial and covered with aluminium foil. This reduced the risk of stray light causing premature homolysis of the photoinitator. Using an IKA VIBREX VXR shaker, set at 200 revs/min for an hour, resulted in a pale orange homogenous solution [Solution B]. 0.2 % w/w of Solution B was added to Solution A. The large glass powder bottle was covered with aluminium foil to prevent premature polymerisation. The pregel was mixed for a further 30 minutes on the orbital shaker, set at 200 revs/min.

A 20 x 15 cm stainless steel tray was lined with silicone coated release paper (non-coated side was face up in the tray). The GEW UV-LAB1 machine was switched on number two the highest power level available, left on for five minutes after which time the pregel was poured into the tray and then placed onto the conveyer belt. The tray was passed under the UV lamp three times which allowed the gel ample time to polymerise. The partially hydrated gel was removed, covered with the silicone coated release paper (non-coated side was in contact with the top of the gel). It was cooled to room temperature for ten minutes. The gel was then stored in a resealable plastic bag until required for further testing.

2.3.2 Mechanical and Physical Characterisation

2.3.2.1 Rheology

Applying a constant force to an ideal solid, which obeys Hookes law of elastic deformation, causes it to deform by a fixed amount. When the force is removed it is expected to regain its original shape. Under similar conditions a gas or liquid would flow (Bohlin Instruments, 1994, Goodwin J.W. et al, 2000). The deformation (elastic) behaviour and the flow (viscous) behaviour form the basis of rheological characterisation. It is possible to diagrammatically depict the stresses (forces) which act on an infinitesimal body of material or the strain rates (flow) that are exhibited:

Simple Deformation under an applied constant force (Hookean response)

A cube of material for example a hydrogel having its base fixed to a surface as shown in figure 2.18 can be used to define the term strain.

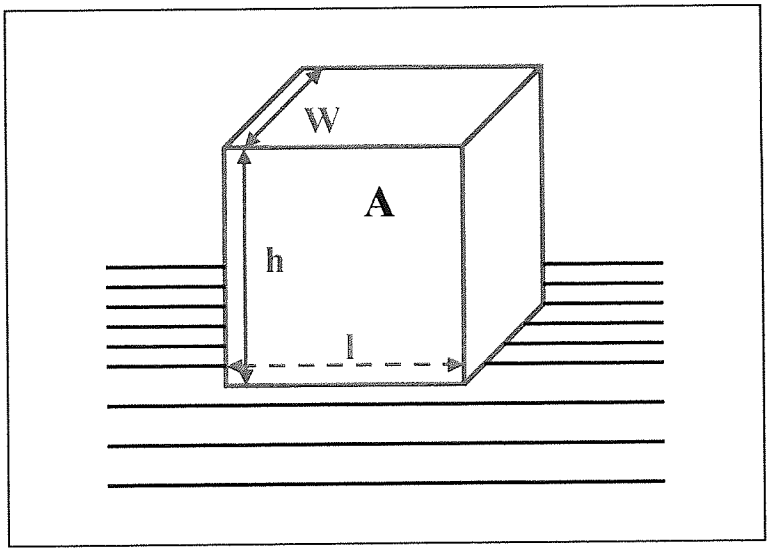


Figure 2.18 A cube of material with its base fixed to the surface

The application of a constant 'pushing' force as shown in figure 2.19 applied to the upper part of the cube, which obeys Hookes law of elastic deformation results in a new position based upon the assumption that the material behaves as an ideal solid. Fixing the lower surface and allowing only the top surface to move, results in deformation, defined as a *shear deformation*.

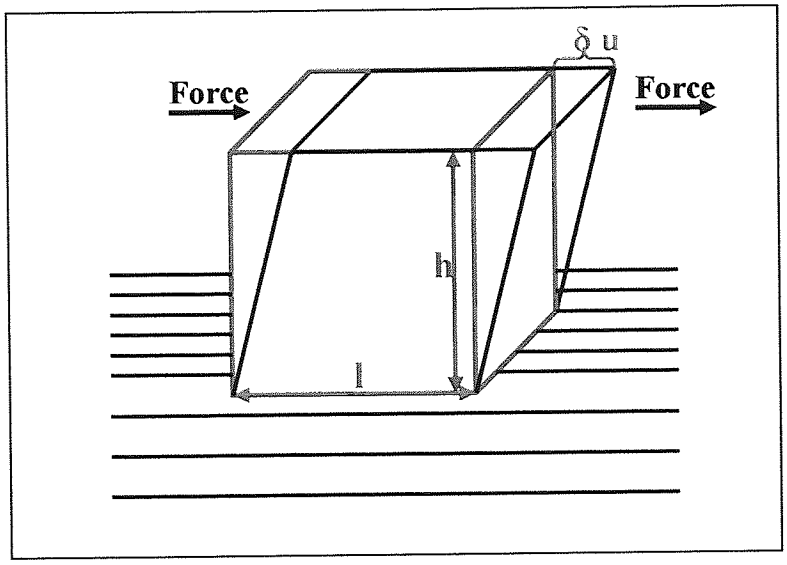


Figure 2.19 Application of a constant force to a cube with a fixed base resulting in shear deformation

The relative deformation also known as the deformation (δ u) per unit length (h) is defined as the *Shear strain* and denoted as ε. This value is a ratio of two lengths and has no units.

$$\text{Shear Strain } \varepsilon = \frac{\delta u \text{ (m)}}{h \text{ (m)}} \qquad (2.1)$$

The amount of *Shear Stress* the cube is subjected to is defined as the force divided by the area over which it is applied (equation 2.2) and has the units of Nm^{-2} also referred to as a Pascal (Pa) denoted by the symbol σ.

$$\text{Shear Stress } \sigma \ (Nm^{-2}) = \frac{\text{Force (N)}}{\text{Area } (m^2)} \qquad (2.2)$$

Hookes law states that stress is proportional to the strain for a purely elastic material. Therefore doubling the stress results in doubling the strain, this shows that the material behaves linearly. The shear modulus, a constant denoted by G, is equal to the stress value divided by the strain value (equation 2.3).

$$G \quad (Nm^{-2}) = \frac{\text{Stress } \sigma}{\text{Strain } \varepsilon} \tag{2.3}$$

Removal of the stress results in the strain returning to zero, assuming no inertia. The material undergoes a fully recoverable deformation so no flow has occurred.

Simple flow under an applied constant shear stress (Newtonian response)

If a cube of material is considered to behave as an ideal fluid the application of shear stress results in a deformation which continually increases at a constant rate (figure 2.20).

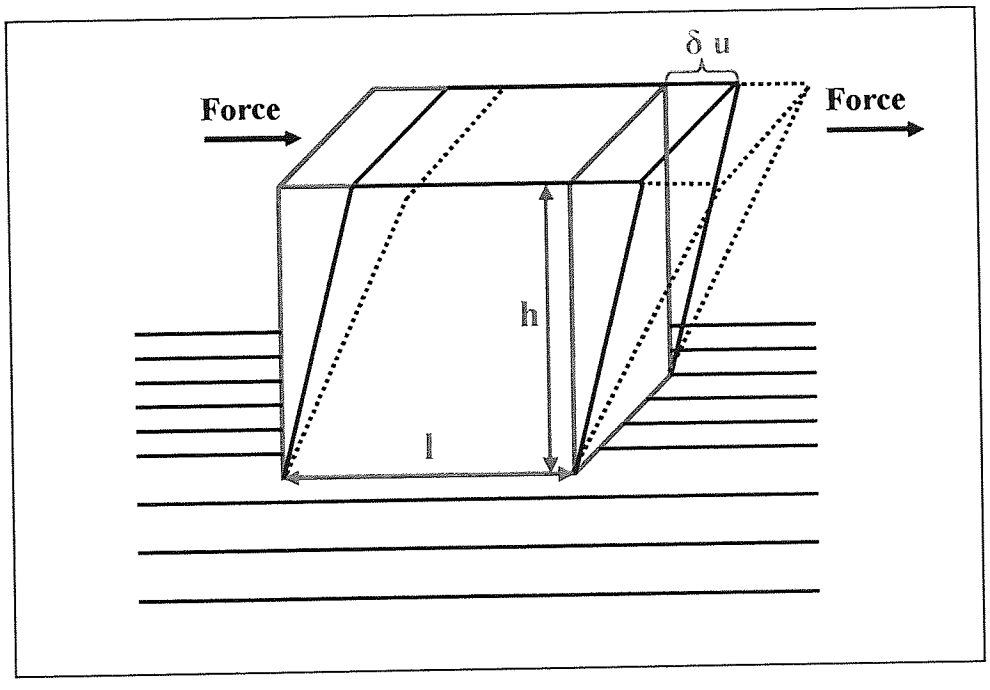


Figure 2.20 A cube of material placed under constant shear stress

The rate of change of strain also known as the shear rate (γ) is quantified as the rate of change of strain ($\delta \varepsilon$) as a function of time (δt) in seconds.

$$\text{Shear Rate } \gamma \ (S^{-1}) = \frac{\delta u\,(m) \times 1}{h\,(m) \times t} = \frac{\delta \varepsilon}{\delta t} \tag{2.4}$$

Resistance to flow is known as viscosity which is directly proportional to the shear stress and inversely proportional to the shear rate (equation 2.5). The units of viscosity (η) are $Nm^{-2}S$ also known as Pascal Seconds (PaS).

$$\text{Viscosity } \eta \ (PaS) = \frac{\text{Shear Stress } \sigma \ (Nm^{-2})}{\text{Shear Rate } \gamma \ (S^{-1})} \tag{2.5}$$

If the viscosity of the material is independent of the shear stress applied then it is referred to as an ideal or NEWTONIAN fluid.

The rheometric measurements required when considering the viscoelastic properties of a skin adhesive hydrogel were achieved by carrying out a strain sweep on the polymer sample which yielded the elastic modulus (G'), the viscous modulus (G'') and the phase angle δ.

The application of a sinusoidally varying stress to a polymer sample will induce a sinusoidally varying strain (vice versa for applied strain). Equation 2.4 and 2.5 show that for a Hookean solid the strain is controlled by the absolute value of the shear stress whereas for a Newtonian liquid the rate of change of strain is controlled by the stress. If a complete cycle of the sine wave is considered as 360° then this can be used to discuss the difference between the two waves also known as phase angle (Bohlin instruments).

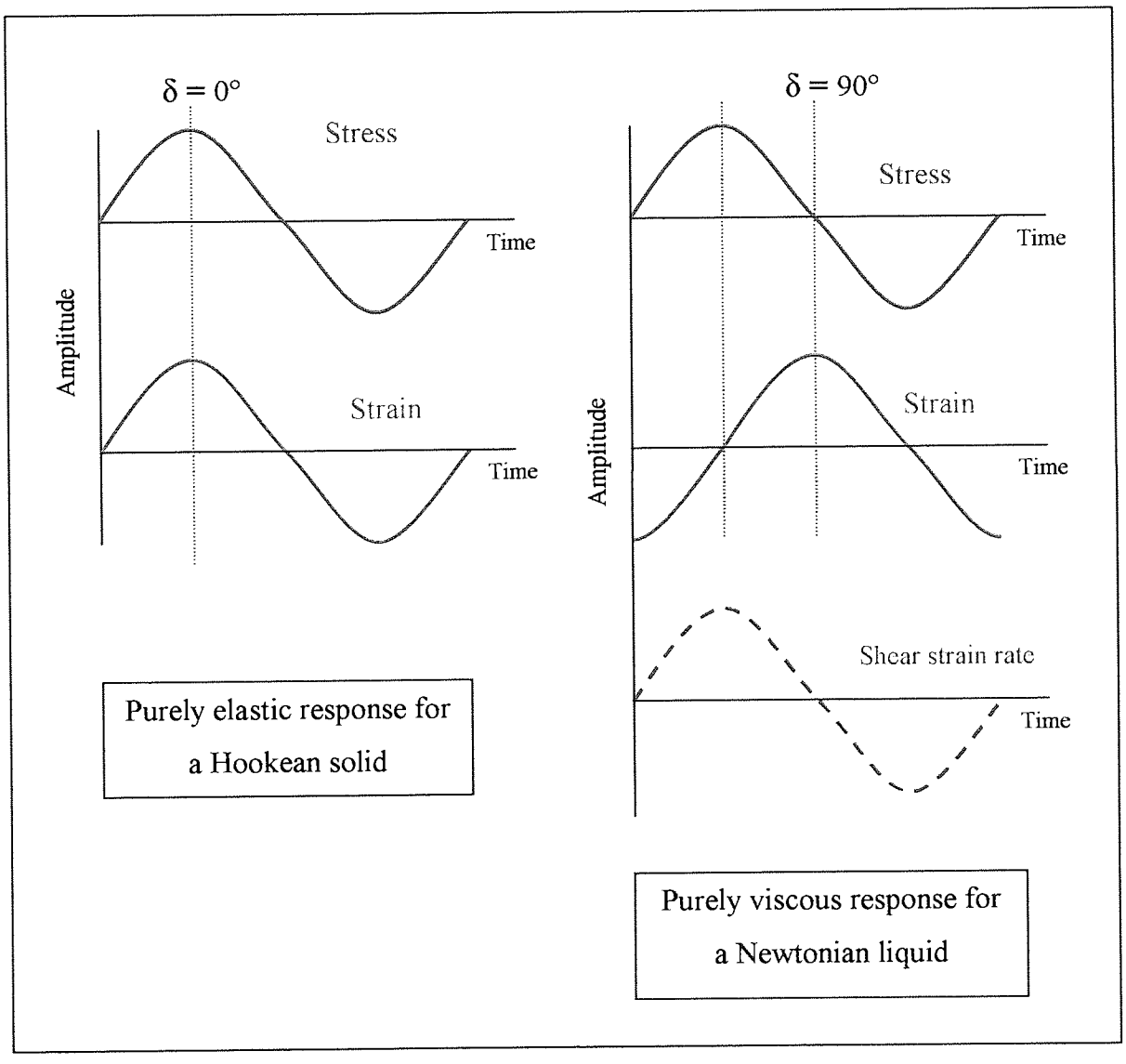


Figure 2.21 Stress/strain responses of a Hookean solid or Newtownian liquid

When considering a pure solid the strain is directly related to the stress and will therefore be at a maximum when the stress is at a maximum and zero when the stress is zero (figure 2.21). The stress response is therefore said to be totally 'in phase' with the applied strain therefore the phase angle will be equal to 0°.

For a purely viscous liquid the shear strain rate is in phase with the stress. A plot of shear strain rate against time shows that the strain alternates between a positive and negative extreme accelerating and decelerating between the two values. When the shear strain rate is at a maximum the rate of change of strain will be zero, hence when the strain is zero the rate of change will be at a maximum. The resultant strain is therefore totally out of phase by 90° to the applied stress. A viscoelastic material has a phase angle that lies between zero and ninety degrees.

Moduli values

As stated in equation 2.3 Hookes law shows the relationship between the strain and stress via a material constant known as *Shear modulus,* G. The stress and strain constantly change in an oscillation test. However, a number of 'instantaneous' values can be utilised to obtain a value of the 'viscoelastic G' and are constant in time for any given frequency. This value is also referred to as the *complex modulus*, G*. This is obtained from the ratio of the stress amplitude to the strain amplitude. The modulus is a measure of the overall resistance to deformation and consists of the two components- the elastic component which is referred to as G' also known as the *storage modulus.* This signifies the elastic storage of energy since the strain is recoverable in an elastic solid. The viscous component denoted by G'' is referred to as the *loss modulus*, which describes the viscous dissipation (or loss) of energy through permanent deformation in flow.

$$G^* = G' + iG'' \tag{2.6}$$

G' and G'' can be defined in terms of sine and cosine functions by measuring the ratio of the stress to the strain (G*) as well as the phase difference between the two (δ).

$$G' = G^* \cos \delta$$

$$G'' = G^* \sin \delta \qquad (2.7)$$

Tan δ is the viscoelastic parameter which gives a measure of the material damping which can be calculated from the storage and loss moduli as shown in equation 2.8.

$$\tan \delta = \frac{G''}{G'} \qquad (2.8)$$

Figure 2.22 Bohlin CVO Rheometer

A Bohlin CVO rheometer (figure 2.22) was used to measure the viscoelastic properties of the sheet skin adhesive hydrogels. A 20mm parallel plate system was used to carry out the appropriate measurements allowing the polymer samples to be sandwiched between

the upper and lower plates. All tests were carried out at 37°C, normal body temperature, allowing the results to be similar to those expected when in vivo. Samples were cut using a size 13 cork borer and then placed onto the upper parallel plate. It was lowered until the sample was in contact with both plates. The hydrogel thickness varied from 1.5 to 2.0mm which produced variations in the gap width.

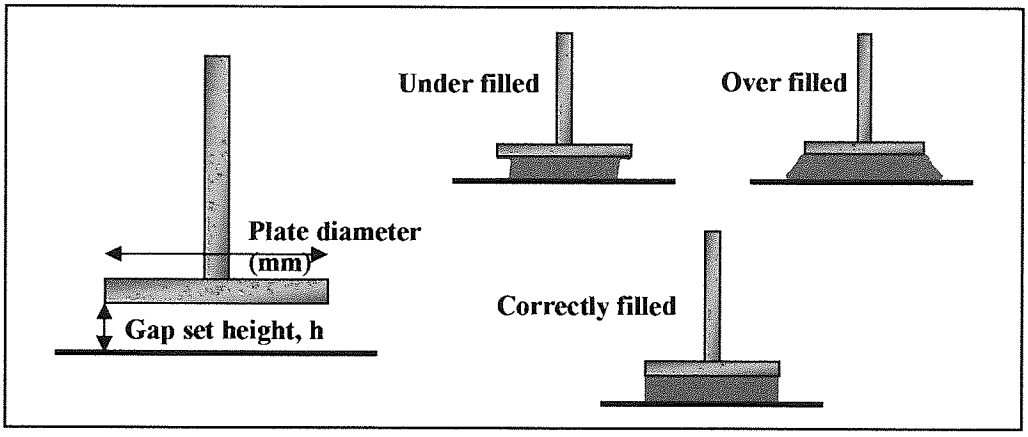


Figure 2.23 Sample loading for a parallel plate measuring system

The sample must be loaded correctly, if there is too little or too much it would result in an incorrect torque leading to the data being too low or too high respectively. The sample was uniformly compressed by the application of a normal force of 5% (100g) throughout the oscillatory sweep. Samples were subjected to a frequency sweep of 0.5Hz to 25Hz. Skin adhesives were subjected to low frequency oscillations to represent long stress time scales. The higher frequencies relate to the short stress times symbolising the removal of the skin adhesive. Experiments were repeated three times with the average results being displayed in further sections. An elastic modulus (G') between 10^3 and 10^5 Pa and a viscous modulus (G'') between 10^2 and 5 x 10^3 Pa (Munro H., 2002) are the range of values expected from a gel possessing good cohesive properties. Ideally, skin adhesives should have a tan δ value less than 1. If the value is more than 1 the viscous behaviour is dominant resulting in the cohesive failure of the gel.

2.3.2.2 Peel Tests at 90 degrees

The shear force required to remove a skin adhesive hydrogel from a substrate can be quantified using a 90° perpendicular peel test. In earlier tests the skin on the forearm was used as the substrate due to its uniform area and ease of accessibility. However a consistent skin condition could not be maintained after a series of tests. Despite carrying out the tests on different areas of the forearm, layers of skin were removed with each test. Time for renewal of the cells in this area had to be allowed before this area could be used again for testing. It was essential to maintain the condition of the substrate, enabling the results to be compared. A system was designed which enabled a substrate to be used without the risk of it being altered from excessive testing. As shown in figure 2.24 a sliding tray containing the substrate (a sheet of smooth stainless steel) was encased in MDF allowing a central area to be exposed, upon which the skin adhesives were attached.

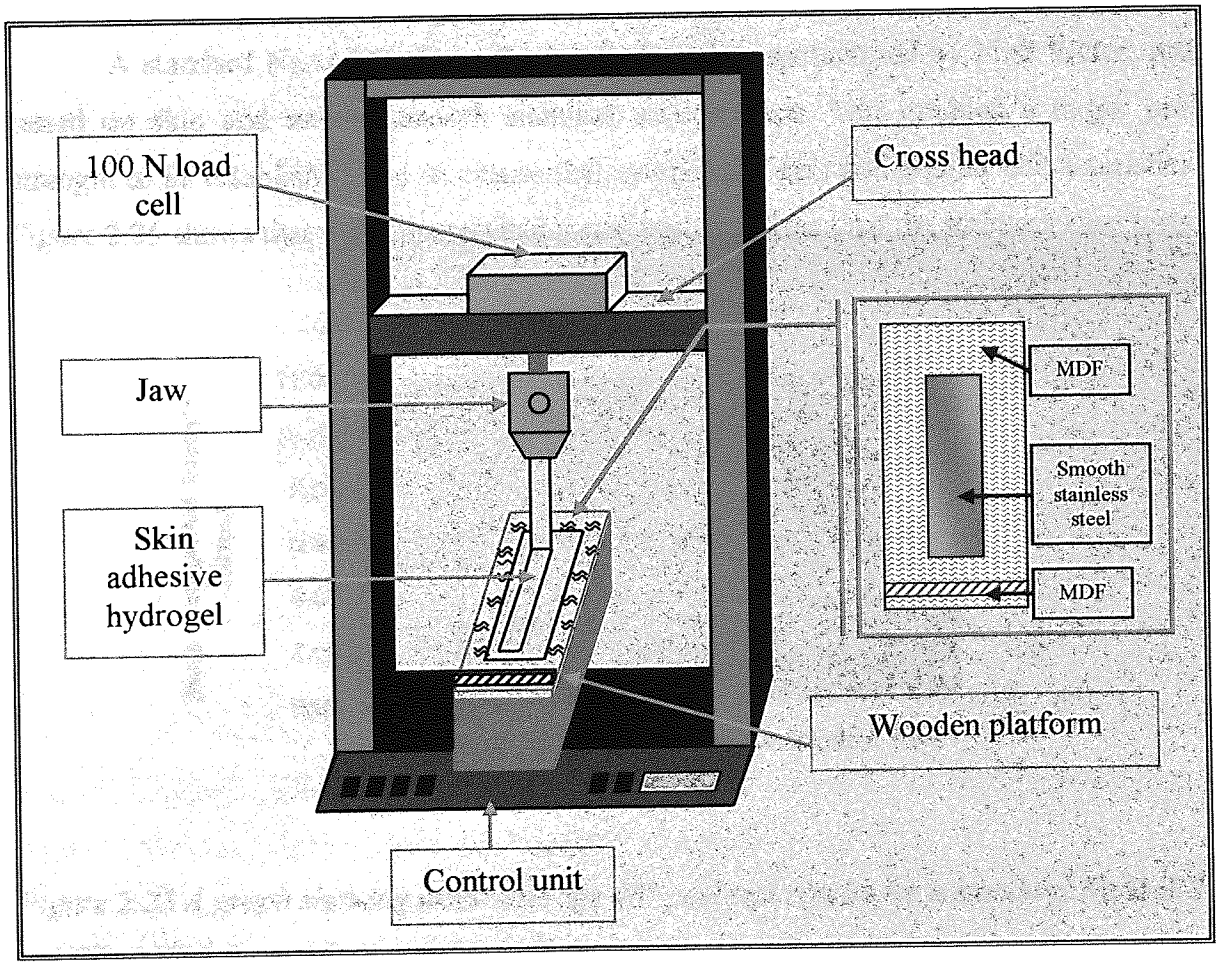


Figure 2.24 Diagram of a Hounsfield Tensometer

Three strips of skin adhesive hydrogel measuring 10cm x 2.5cm (4"x 1") were tested and the average result was recorded and used in further sections. A strip was pressed onto the stainless steel sliding tray with a small amount of sample left off the tray. This was clamped in the jaws of the tensometer. The strip was peeled from the substrate, at a rate of 500mm/min, as the tray was moved horizontally forward ensuring that the sample removed was at 90°. A 100N load cell was used for all the peel tests and the data was relayed to the computer software, which calculated the peel strength in N/25mm, for each sample. Ideally the peel strength value can be used to evaluate whether sufficient adhesion had occurred. The application of a large force to remove the strip indicated that adhesion was strong. A balance was necessary to ensure that the gel adhered to the skin for the required time and minimal discomfort was felt by the removal of the top layer of dead skin.

A standard NaAMPS skin adhesive hydrogel, manufactured by First Water, was tested on skin and on the smooth stainless steel surface. This enabled a target peel strength to be established and to ensure that synthesised gels had similar characteristics. Figure 2.25 shows that the skin tests had lower peel strengths than the stainless steel tests.

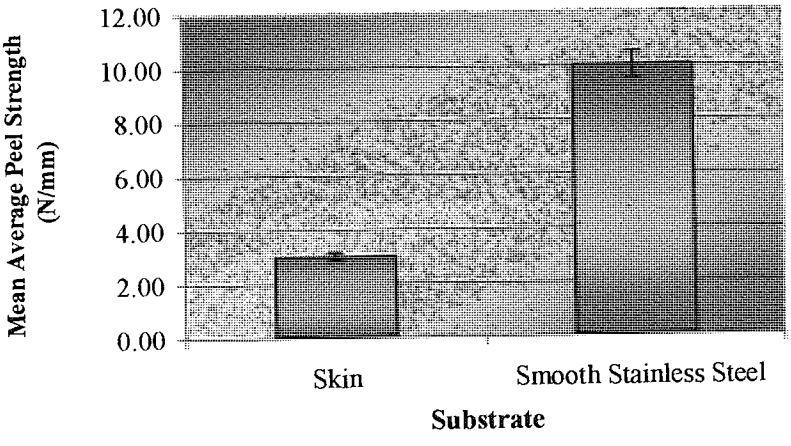


Figure 2.25 A graph showing mean average 90° peel test results for a standard NaAMPS gel (First Water) on different substrates

2.3.2.3 Optical microscroscopy

A Leitz Dialux 20 light microscope with a MPS Wild camera attachment was used to investigate the surface morphology of skin adhesive hydrogels. The sample was mounted on a glass slide and stained with a saturated solution of bromopyrogallol red in methanol. It was clamped between the metal supports on the stage and held in place with the small clips. The eyepieces were then moved in either a clockwise or anticlockwise direction until an image was visible. A downward movement of the stage allowed the image to be focussed. A photograph was taken by the MPS 15/11 photomicrography unit on a 35mm roll of film. To ensure that that there was enough light to take a photomicrograph it was adjusted at the external light unit (the green light indicated that the level of lighting was adequate).

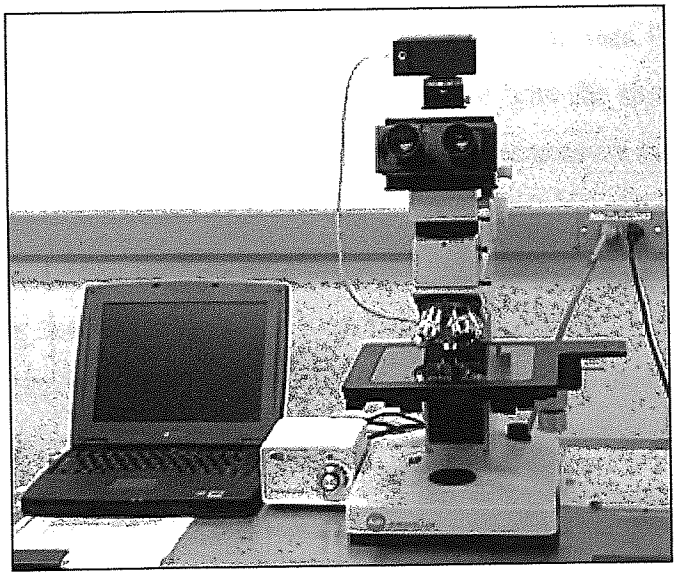


Figure 2.26 Optical microscope

An alternative method of staining was available for the biphasic gels. This involved the incorporation of oil red o within the formulation, at the time of synthesis. This technique allowed the hydrophobic domains to be seen with ease.

2.3.2.4 Dynamic Vapour Sorption (DVS)

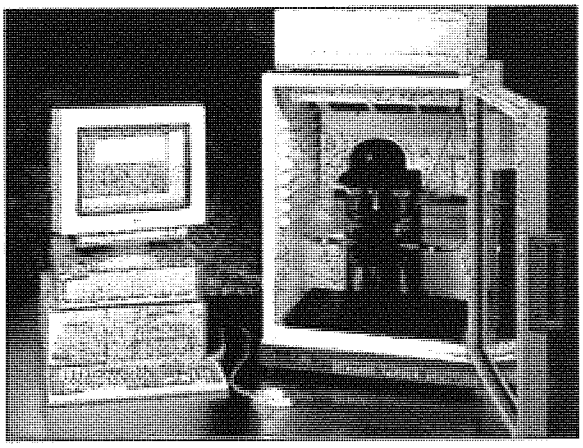


Figure 2.27 DVS instrument

Scientific & Medical DVS was used to determine the rate at which vapour sorption or desorption occurred in the gels on varying the humidity. It was used to measure the hygroscopic properties of each formulation to determine how the skin adhesives behaved under different conditions. The relative humidity was generated by bubbling N_2 through a water reservoir which is saturated with moisture. In the mixing chamber the wet N_2 was mixed with dry N_2 at a fixed ratio to give the required relative humidity. As illustrated in figure 2.27 and 2.28 the DVS contains two sample chambers. The reference chamber contained only an empty pan while the other contained the material being monitored, under different conditions. Both sample pans were connected to a highly sensitive CAHN microbalance, located in the temperature controlled chamber, which was set to 37°C. Before any experiments were conducted the relative humidity was initially set to 20% and the balance was zeroed, with no sample present. Each sample was cut using a size 2 cork borer and weighed less than 100mg. The sample was carefully placed onto the pan at which point the mass registered in the DVS software. Samples were subjected to the preset relative humidity conditions. The sample would either take up moisture, causing an increase in the flow of dry N_2 or it would lose water which meant that moisture was being lost and therefore the humidity would increase. Stabilisation of the mass indicated that equilibrium had been reached.

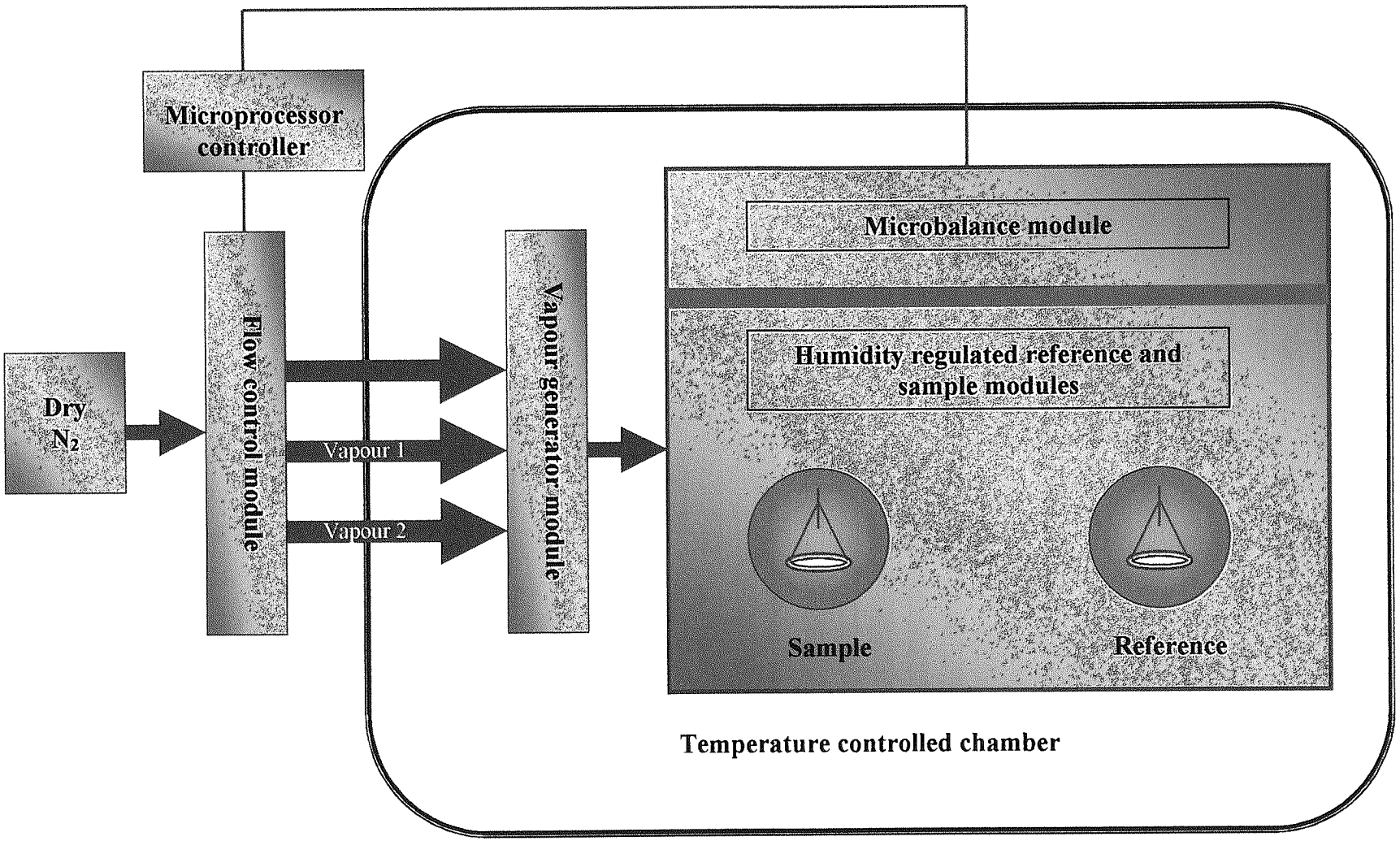


Figure 2.28 Schematic diagram of DVS flow stream of controlled humidity

2.3.2.5 Equilibrium water content (EWC) of fully hydrated hydrogels

Dehydrated non adhesive gels polymerised using one of the methods shown in section 2.3.1 were fully hydrated by placing them into distilled water for five days giving the gel ample time to reach its equilibrium water content. The water was changed daily to ensure the removal of residuals. Using a size five cork borer four sample of the gel were cut and weighed. These values were recorded to four decimal places. The samples were placed on a clean heat proof block in the microwave oven. The water was removed and the gels were weighed until a constant weight was achieved, signifying that the gel was fully dehydrated. Using equation 2.15 the equilibrium water content (EWC) was calculated for all four samples with the average being used in results shown in chapter 4.

$$\text{EWC } \% = \frac{[(\text{hydrated weight} - \text{dry weight})]}{\text{hydrated weight}} \times 100 \qquad (2.15)$$

2.3.3 Analytical technique - Ultraviolet- Visible Spectroscopy (UV-Vis spectroscopy)

Most organic molecules and functional groups are transparent in the ultraviolet (UV) and visible (Vis) regions of the electromagnetic spectrum, where the wavelengths range from 190nm to 800nm (Harwood L.M. et al, 1989, Settle F.A., 1997). When continuous radiation is passed through a transparent material, a portion of the radiation may be absorbed. The residual radiation is passed through a prism which yields a spectrum with gaps in it, referred to as the absorption spectrum. Upon energy absorption atoms and molecules pass from a state of low energy (ground state) to one of higher energy (excited state). The quantised excitation process is depicted in figure 2.29. The energy difference (Δ E) between the excited and ground states is exactly equal to the amount of electromagnetic radiation that has been absorbed.

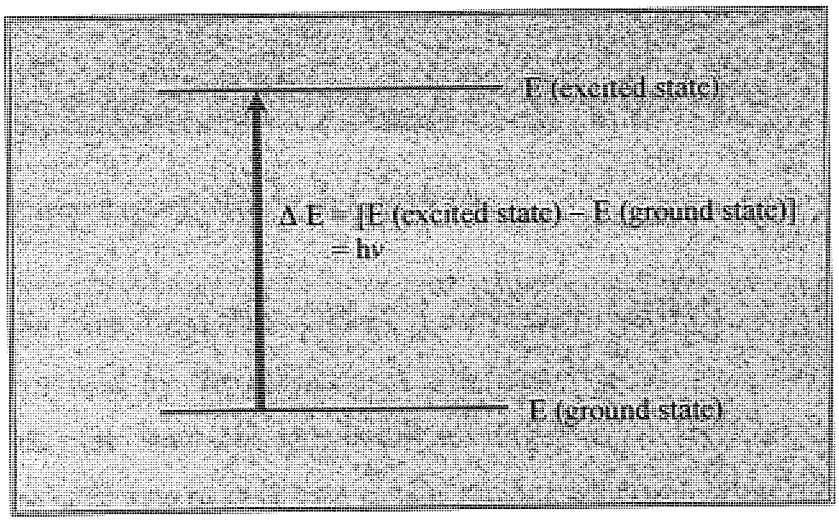


Figure 2.29 The excitation process

Emphasis is placed upon the transitions that occur between electronic energy levels. Absorption of energy by a molecule can result in the promotion of an electron from an occupied orbital to an unoccupied orbital of greater potential energy. This is typically from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). The sigma orbitals are the lowest energy occupied molecular orbitals and pi orbitals lie at higher energy levels. Orbitals possessing unshared electrons are known as non bonding (n) and lie at even higher energies. Antibonding orbitals (π^* and σ^*) as shown in figure 2.30 lie at the highest energy levels. A substantial amount of

absorption spectroscopy on organic compounds is based upon the transitions of the n or π electrons to the excited state, π^*.

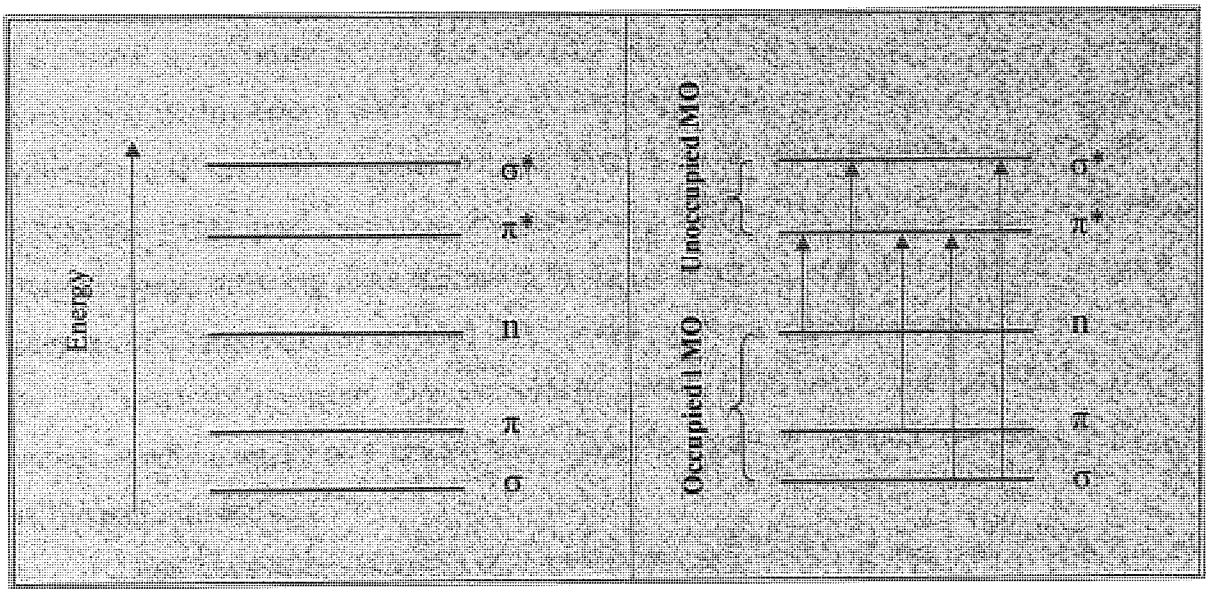


Figure 2.30 Electronic energy levels and transitions

Absorption peaks range from 200 - 700nm, a convenient region of the spectrum. The π electrons are provided by the presence of unsaturated groups e.g. alkenes, carbonyl compounds or alkynes. Saturated compounds containing either oxygen, nitrogen sulphur or halogen atoms have lone pairs known as non bonding electrons, are capable of the n → σ^* transitions. Light ranging from 150 – 250 nm can initiate this process and the number of organic functional groups with this peak, in the UV region, is small. The presence of a carbonyl group in a chemical compound results in a $\sigma \rightarrow \pi^*$ transition being detected. An electron in a bonding σ orbital can be excited to its corresponding antibonding orbital. However, the energy required for a transition $\sigma \rightarrow \sigma^*$ is large when compared to other transitions. For example methane has only C-H bonds and shows an absorbance maximum at 125nm. This type of transition is not typically seen in the UV–Vis spectrum. The n → π^* transition has a lower energy when compared to a $\pi \rightarrow \pi^*$ transition. Not all of the transitions are possible; the spin quantum number of an electron is required to change during a transition and if it is not allowed it is known as a forbidden transition.

The symmetry properties and electronic states need to be considered for electrons excited at any given time. Transitions that are formally forbidden are often not observed. Theoretical treatments yield approximations and in certain cases forbidden transitions can be observed. The intensity of the absorption tends to be much lower than the allowed transitions, in accordance with the selection rules. When a molecule absorbs UV light, absorption occurs over a wide range of wavelengths, due to the many excited modes of vibration and rotation at room temperature. A molecule can undergo electronic and vibrational - rotational excitation simultaneously. There are a large number of transitions possible, each differing from the other by slight amounts, and each electronic transition consists of a large number of lines that are spaced close together that cannot be resolved by the spectrophotometer. The instrument traces an envelope over the entire pattern which usually consists of a large broad band of absorption, centered near the wavelength of the major transition.

Light absorption occurring at a greater intensity occurs if there are a large number of molecules capable of absorbing light, of a given wavelength. The effectiveness of a molecule absorbing light of a given wavelength depends upon the extent of light absorption and the following empirical equation known as the Beer - Lambert Law:

(2.14)

$$A = \log (I_o/I) = \epsilon c l$$

A= absorbance

I_o= intensity of light incident upon the sample cell

I = intensity of light leaving the sample cell

ϵ = molar absorptivity (L mol^{-1} cm^{-1})

c = molar concentration of solute (mol L^{-1})

l = length of sample cell (cm)

The molar absoptivity is known as the molar extinction coefficient. It is a property of the molecule undergoing an electronic transition and is not a function of the variable parameters involved in sample preparation. The absorptivity, which ranges from 0 to 10^6, is controlled by the size of the absorbing system and the probability that the electronic

transition will take place. High intensity absorptions give values above 10^4. Values below 10^3 are classed as low intensity absorptions. Forbidden transitions have absorptivities in the range 0 to 1000. When a single species gives rise to the observed absorption the Beer – Lambert law is rigorously obeyed. The law is not obeyed if different forms of the absorbing molecule are in equilibrium, for example when solute and solvent form complexes through some sort of association. If thermal equilibrium exists between the ground electronic state and a low lying excited state or compounds that change by irradiation, it will not be obeyed.

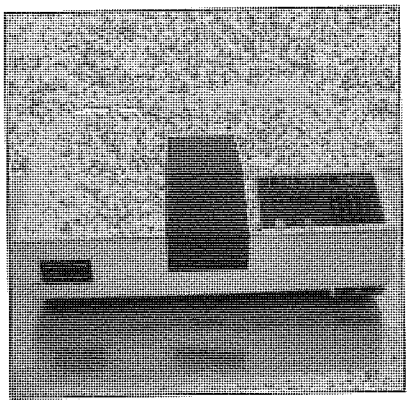


Figure 2.31 UV-Visible spectrometer

The UV-Visible spectrophotometer (figure 2.31) consists of a light source, a monochromator and a detector. A deuterium lamp is the light source and it emits electromagnetic radiation in the ultraviolet region of the spectrum. A second light source is required to emit the wavelengths of light corresponding to the visible region of the spectrum and therefore a tungsten lamp is employed. A diffraction grating, known as the monochromator, is used to separate the beam of light into its component wavelengths. A system of slits focuses the desired wavelength on the sample cell. The intensity of light that passes through the sample and reaches the detector is recorded as the intensity of transmitted light (I). In typical double beam instruments the light emanating from the light source is split into two beams, the sample and the reference beam. If there is no sample in the reference beam cell, the detected light is taken to be equal to the intensity of light entering the sample (I_o). The sample cell needs to be constructed from a material which is transparent to electromagnetic radiation. Quartz cells are ideally used especially

when looking at the ultraviolet region since glass or plastic cells are capable of absorbing the radiation.

The functional groups responsible for UV or visible absorption are known as chromophores. They have the ability to exhibit the electronic transitions shown in figure 2.30. In order to observe a $\pi \rightarrow \pi^*$ transition there must be a molecular group containing a double bond (e.g. carbonyls and azo compounds). To observe an $n \rightarrow \pi^*$, nonbonding electrons and a double bond must be present (e.g. carbonyls, nitro or azo groups). Molecules exhibiting $n \rightarrow \sigma^*$ transitions have a single bond and non bonding electrons (e.g. alcohols, amides and water).

2.3.4 Inhibitor removal

Hydroquinone (HQ) and mono methyl ether hydroquinone (MEHQ) are two common inhibitors found in vinyl and acrylic based monomers. They promote the process and shelf life stability by abstracting a hydrogen radical from chain radicals. During monomer production via free radical polymerisation, side reactions can occur resulting in the generation of hydroperoxides. They decompose over time forming alkoxy chain radicals and hydroxy radicals which can lead to premature polymerisation. The inhibitor will react with chain radicals and prevent further reactions with other unsaturated sites resulting in the termination of chain propagation. A stabilised HQ results from the delocalisation of the electron charge density throughout the aromatic structure. Although the stabilised HQ radical cannot initiate polymerisation it can react with additional radicals to terminate propagation. Generation of hydroquinone and quinone occur when two HQ radicals react with each other. Removal of the inhibitor enables polymerisation to take place at a faster rate compared to monomer containing higher levels. A quick, simple method used to remove the inhibitor from the monomers was with a prepacked inhibitor column. Monomer used in the synthesis of partially hydrated adhesive hydrogels will come in contact with the skin. Therefore HQ must be removed to prevent depigmentation. This is not acceptable for people who have higher levels of melanin in their skin.

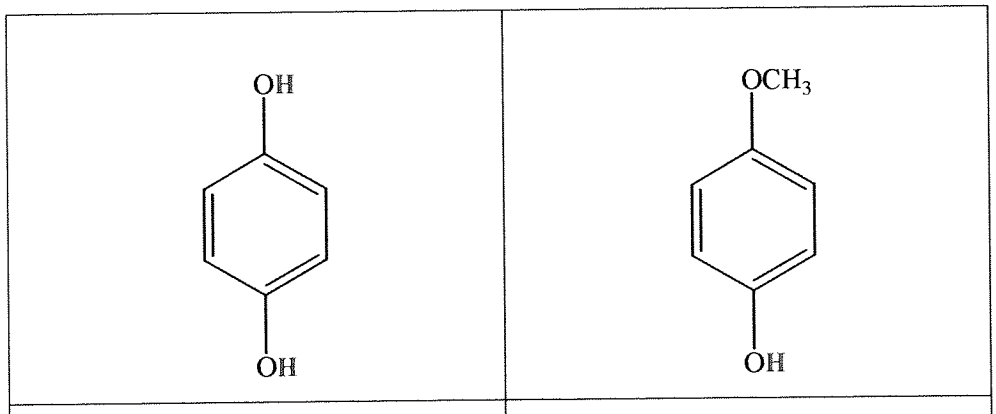


Figure 2.32 Chemical structures of hydroquinone and mono methyl ether hydroquinone

A 9 x 0.8" prepacked column, from Aldrich, was used to remove the HQ/MEHQ from the

monomer (AMO or epoxidised soyabean oil acrylate). The apparatus was assembled as shown in figure 2.33. The epoxidised soyabean oil acrylate was extremely viscous and 30g of the monomer was diluted in 80ml of diethyl ether to ensure that the solvent did not interfere with the packing. The monomer-solvent solution was transferred into an addition funnel. The solution was passed through the column slowly ensuring that overflow was prevented. The monomer was given ample time to pass through the column ensuring that the inhibitor levels were reduced. The solution was collected in a one necked 200ml round bottomed flask. The solvent was removed by rotary evaporation. The resulting monomer was stored in a refrigerator until required. Some monomers for example NVP or AMO were passed down the column neat because they were less viscous than ESBA.

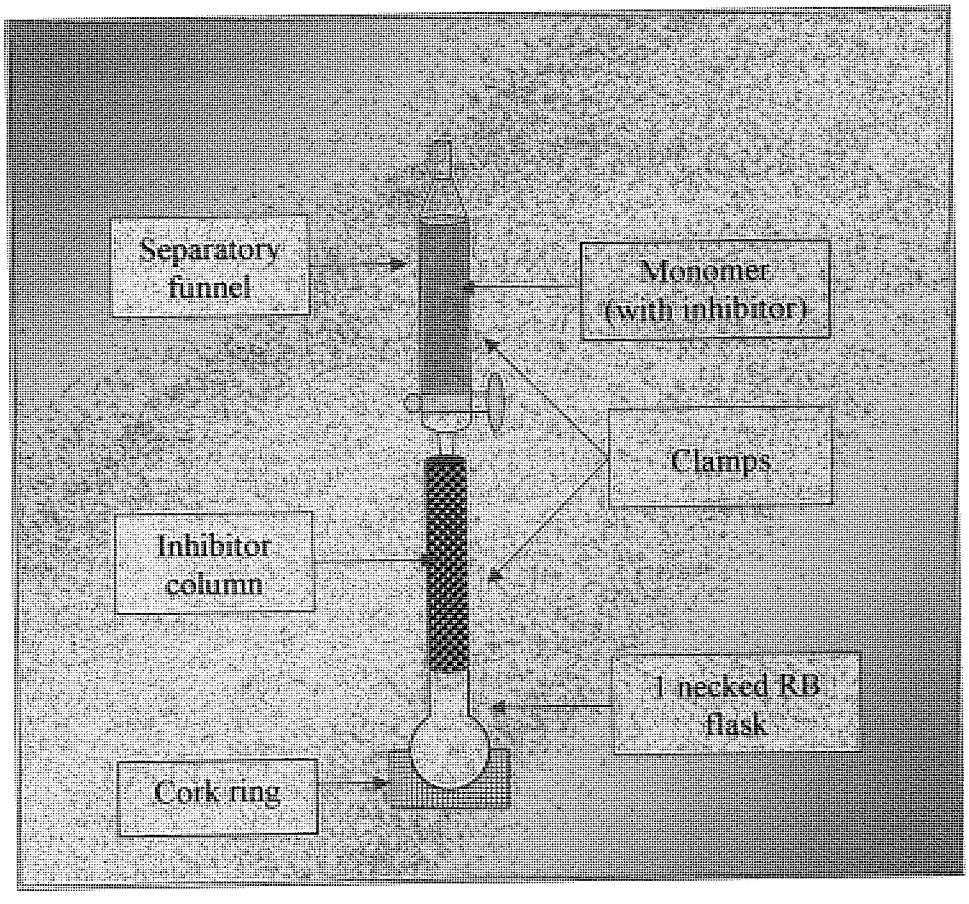


Figure 2.33 Removal of an inhibitor from a monomer

Chapter 3

Photopolymerisation &

Monophasic Gel Technology

3. Introduction

3.1 Photopolymerisation

Photopolymerisation is widely used by the electronic, packaging and printing industries. This technique allows the formation of polymers via a simple method with the focus on free radical chain addition. Initiation is the first step in the formation of radicals by an external stimulation UV radiation. Light induced photopolymerisation has several advantages over the other methods including controllability via selective wavelength irradiation and light intensity. This technique has outstanding benefits which range from a system with low or no volatile organic compounds to a boost in productivity. The process of free radical photopolymerisation consists of a series of steps as shown below (Billmeyer F.W. Jr, Cowie J.M.G., 1991, 1984, Flory P.J., 1953, Young R.J. et al, 1991):

- *Initiation*

This involves a two step process the first is the creation of active centres (free radicals) via the input of an external source of energy. A free radical is an atomic or molecular species whose normal bonding system has been modified. Equation 3.1 below shows that UV light is required to decompose the photoinitiator to yield a pair of free radicals.

$$I \xrightarrow{hV} 2R\bullet \qquad (3.1)$$

The second step of this process involves the reaction of a primary free radical (R •) with an olefinic monomer to generate a chain carrier. The special reactivity of the π bonds in the monomer makes it susceptible to rearrangement if activated by free radicals.

$$R\bullet + M \rightarrow RM_1\bullet \qquad (3.2)$$

The activity is retained in order to propagate a macromolecular chain under appropriate conditions. Not all of the primary radicals will result in chain radicals (RM_1 •) in accordance with equation 3.2 some may be lost in side reactions for example recombination of primary free radical species.

- *Propagation*

Successive addition of monomers (M) to radicals ($RM_n\bullet$) results in the growth of the macromolecular chain via a kinetic chain mechanism in a long sequence of identical events as shown below.

$$RM_1\bullet + M \rightarrow RM_2\bullet \quad (3.3)$$

$$RM_2\bullet + M \rightarrow RM_3\bullet \quad (3.4)$$

$$RM_n\bullet + M \rightarrow RM_{n+1}\bullet \quad (3.5)$$

Chain propagation is a rapid procedure with the average life of growing chains being short lived. A chain over 1000 units can be produced in 10^{-2} to 10^{-3} seconds.

- *Termination*

Free radicals are particularly active species and the bimolecular reaction between a pair of free radical chains ($M_m\bullet$ and $M_n\bullet$) results in the annihilation of the active centres which brings the kinetic chain to a halt (Flory 1953, Young et al 1991).

$$M_m\bullet + M_n\bullet \rightarrow M_{m+n} \quad (3.6)$$

A high radical concentration results in the production of short chains since the probability of radical interactions is high. In order to achieve long chains the radical concentration needs to be kept at a low level. There are various routes by which termination takes place:

- Coupling of two active chain ends also known as combination
- An active chain end reacts with a radical, yielding a polymer and does not have a shorter chain length when compared to the polymer formed by the coupling process
- Abstraction of a hydrogen atom from one growing chain by another in a process known as disproportionation
- Interaction with impurities or inhibitors

3.1.1 Photoinitiation

The chemical characteristic of a photoinitiator governs the mechanism of radical generation and it occurs through two possible pathways Norrish I or Norrish II (Ciba G., 1995, Stevens M.P, 1990).

- *Norrish I type – intramolecular bond cleavage*

The α- cleavage photoinitiators (e.g. acetophenone and derivatives) generate radicals by undergoing intramolecular (homolytic) bond cleavage upon the direct absorption of light. The fragmentation leads to the formation of free radicals and from a chemical kinetics point of view this is a unimolecular reaction. The quantum yield of radical formation ($\Phi_{R\cdot}$) is the term given to the number of initiating radicals formed upon the absorption of one photon:

$$PI \xrightarrow{h\nu} PI^* \xrightarrow{k} R^{\cdot}_1 + R^{\cdot}_2 \tag{3.7}$$

$$\frac{d[R^{\cdot}_1]}{dt} = \frac{d[R^{\cdot}]}{dt} = k\,[PI^*] \tag{3.8}$$

$$\Phi_{R\cdot} = \frac{\text{number of initiating radicals formed}}{\text{number of photons absorbed by the photoinitiator}} \tag{3.9}$$

Theoretically, Norrish I type photoinitiators should have a $\Phi_{R\cdot}$ value of 2 because two free radicals are formed via the photochemical reaction. There are various deactivation routes of the photoexcited initiator for example fluorescence or non radiative decay and energy transfer from the excited state. Usually one of the two of the radicals formed will add to the monomer which initiates polymerisation whereas the other radical undergoes either combination or disproportionation.

The excitation energy of a photoinitiator needs to be greater than the bond dissociation energy but still high enough in order to guarantee long term storage stability. Norrish type I photoinitiators are aromatic carbonyl compounds with appropriate substituents.

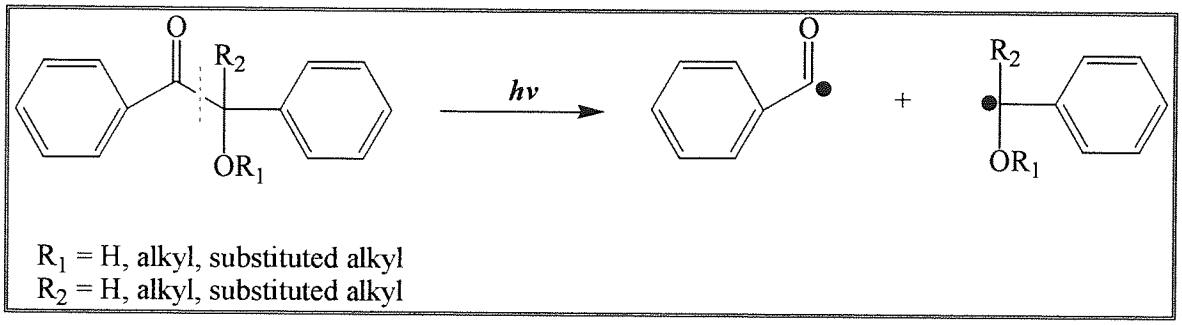


Figure 3.1 Norrish I type photoinitiator

The wavelengths of UV to induce dissociation range between 240-250 nm and 325-333nm. The initiator triplet state is of importance and this is the starting point of α-cleavage.

- *Norrish II type – intermolecular hydrogen abstraction*

Norrish II type photoinitiators are dissimilar to type I photoinitiators since their excitation energy is not high enough for fragmentation to take place; their excitation energy is lower than their bond dissociation energy. The excited molecule reacts with a coinitiator (COI) to produce initiating radicals and follows second order chemical kinetics.

$$PI \xrightarrow{h\nu} PI^* \tag{3.10}$$

$$PI^* + COI \xrightarrow{k} R^{\cdot}_1 + R^{\cdot}_2 \tag{3.11}$$

$$\frac{d[R^{\cdot}_1]}{dt} = \frac{d[R^{\cdot}_2]}{dt} = k\,[PI^*]\,[COI] \tag{3.12}$$

Hydrogen abstraction from a suitable donor, for example the photo reduction of benzophenone, as shown in figure 3.2, is a distinct pathway of radical generation.

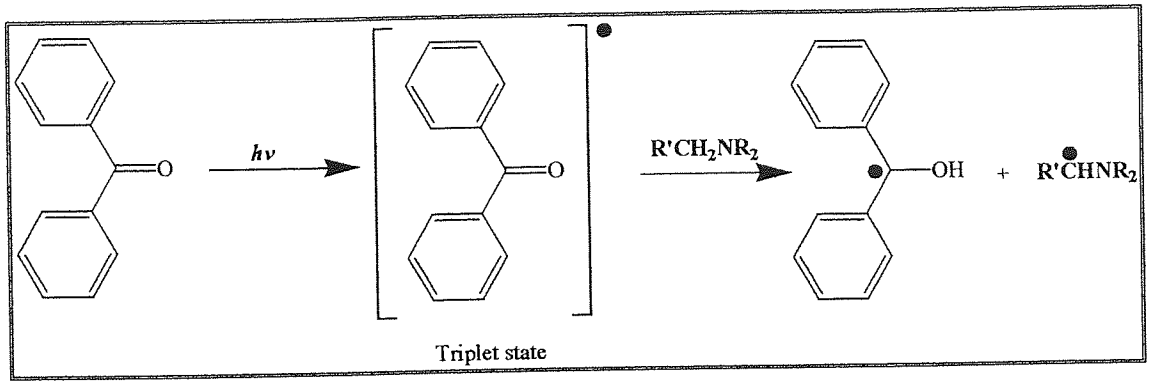


Figure 3.2 Norrish II type photoinitiator

The hydrogen transfer photoinitiators (e.g benzophenone and derivatives) entail a bimolecular process and require the presence of a hydrogen donating source for the generation of free radicals. Tertiary amines with abstractable – hydrogen atoms are effective hydrogen donors for the UV curing of acrylate monomers.

3.2 Photophysics

The first step of photoinitiated polymerisation is the absorption of light energy by the photoinitiator. It is essential that the absorption bands of the photoinitiator overlap the emission bands of the light source in order to produce the reactive species. They are required to activate sequential processes.

Photopolymerisation was carried out using a GEW Laboratory UV Curing Unit. The bench top curing unit consisted of a stainless steel mesh belt, which transported samples under the UV lamp, at speeds ranging from 0.1 m/min to 70m/min. The whole unit was cooled by a powerful exhaust fan which allowed many hours of continuous operation. The intensity of the UV light was variable. It was altered by selected the power level either 40 / 70 / 100 W/cm.

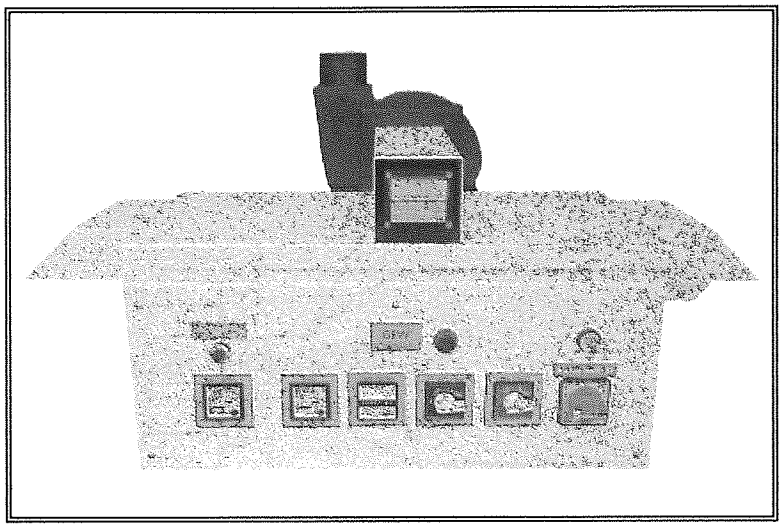


Figure 3.3 GEW Laboratory UV Curing Unit

A medium vapour pressure mercury arc lamp generated the UV light required for this type of polymerisation. It is used commercially for photocuring inks and coatings (Aquionics, 2006). The lamp shown in figure 3.4 was constructed of a sealed quartz tube and allowed 90% of the ultraviolet light to be emitted. Normal silica glass filters out only the weaker wavelengths of light. Under normal operating conditions the surface temperature of the lamp can reach between 600°C and 800°C. Quartz can withstand these temperatures since it has a very high melting point and very low thermal expansion characteristic. A high voltage arc is sustained between the tungsten electrodes at each end and is over wound with tungsten wire. The temperature of the arc reaches over 3000°C and the tungsten electrodes withstand this condition. Molybdeum foil connects the electrode inside the lamp to the power supply outside due to its low coefficient of expansion. It is capable of carrying the high voltage required to sustain the arc. Electrical insulation at the ends of the lamp is achieved by the ceramic end fittings. Mercury vapour pressures range from 100 to several hundred kPa. Figure 3.5 shows the distribution of power, used to produce infrared, visible and the UV radiation of which the latter is the most relevant source of energy for the photopolymerisation process.

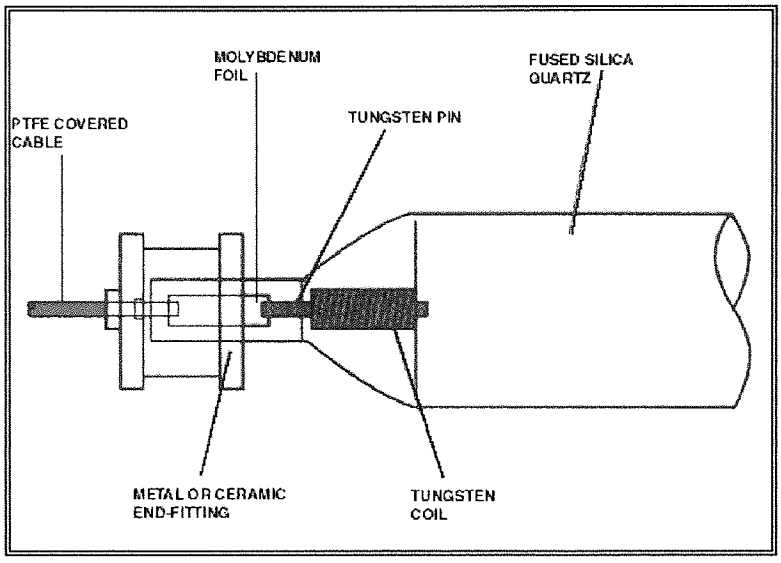


Figure 3.4 A typical Medium Pressure Mercury Arc Lamp

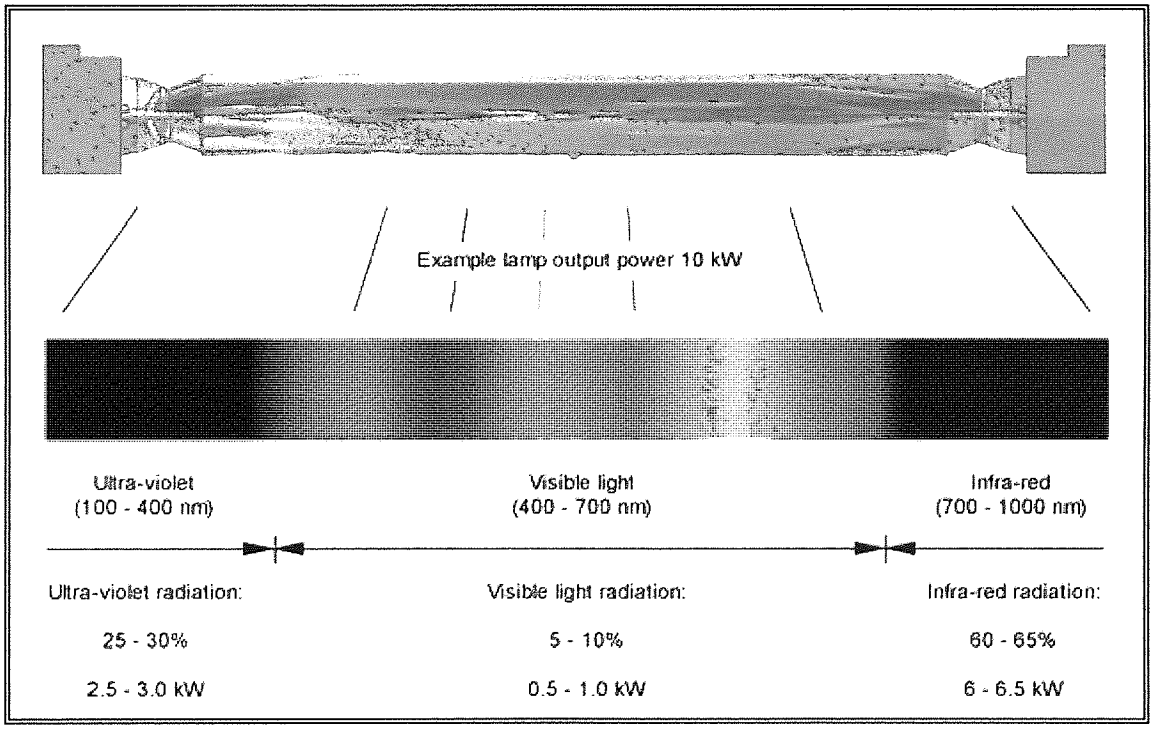
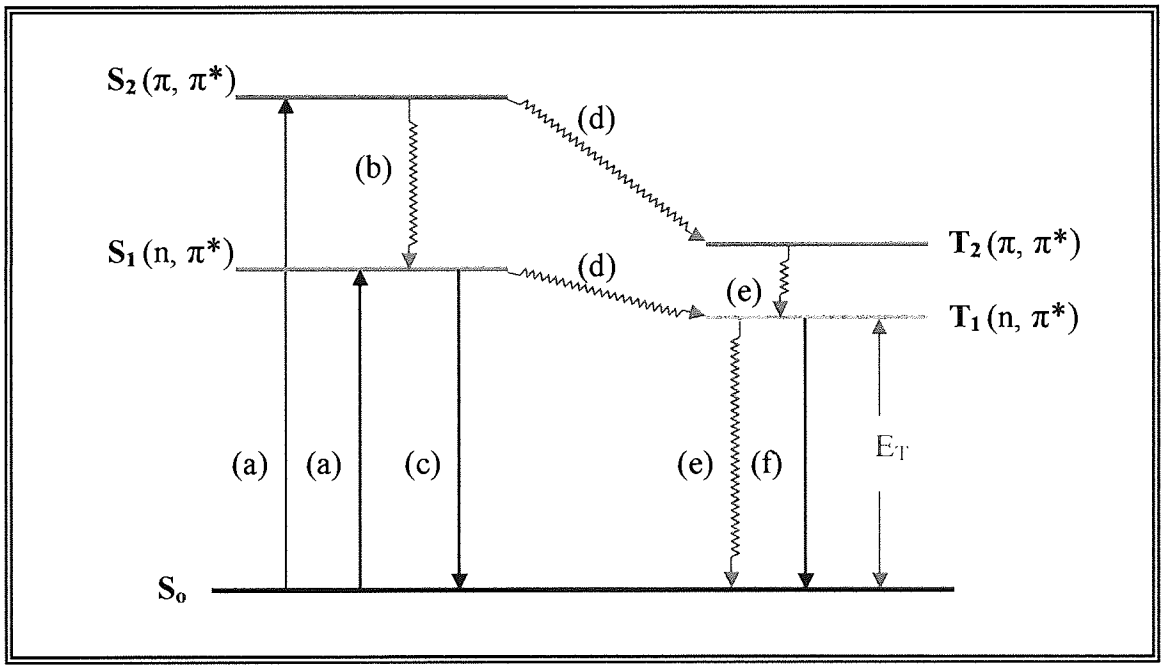


Figure 3.5 A typical medium pressure mercury discharge lamp power distribution

3.2.1 Intersystem Crossing and the nature of excited states

Most molecules in their ground state possess an even number of electrons which are spin paired. Promotion of these electrons from their ground state has a dramatic effect on the reactivity. The molecule that possesses more energy will have the ability to participate in different reactions, as a result of the new electronic arrangement. A typical energy level diagram for aromatic ketones is shown in figure 3.6. Ground state singlets (S_o energy level) can be excited by the absorption of light promoting the electron to the excited singlet state (either $S_1(n, \pi^*)$ or $S_2(\pi, \pi^*)$ energy levels), which can then undergo spin unpairing to yield their respective excited state triplets (either $T_1(n, \pi^*)$ or $T_2(\pi, \pi^*)$ energy levels).



(a) Light absorption	S_o	Ground state
(b) Singlet decay (Radiationless)	S_1, S_2	Excited singlet states
(c) Singlet decay (Fluorescence)	T_1, T_2	Excited triplet states
(d) Intersystem crossing	⟶	Radiative process
(e) Triplet decay (Radiationless)	⇢	Radiationless process
(f) Triplet Decay (Phosphorescence)	E_T	Triplet energy

Figure 3.6 A typical energy level diagram for aromatic ketones

Excited species prefer to relax to a lower vibrational energy state, the ground state via singlet decay or intersystem crossing, which is the loss of energy in the absence of light emission. This process will take pico seconds or less. The excessive amount of vibrational energy arising from the significant number of vibration cycles which transpire during the excited states is converted into heat. An excited molecule exists in the lowest excited singlet state (S_1), for periods of the order of nanoseconds (the longest time period in the fluorescence process by several orders of magnitude), before finally relaxing to the ground state. If relaxation from this long-lived state is accompanied by the emission of a photon, the process is formally known as fluorescence. The importance of the triplet state is the high degree of chemical reactivity exhibited by molecules, which often results in photobleaching and the production of damaging free radicals. Transitions from the triplet excited state to the singlet ground state are forbidden. This results in the rate constants for triplet emission being several orders of magnitude lower than those for fluorescence (Hageman H. J., 1991).

3.3 Monophasic Technology

Monophasic technology is the term used to describe hydrogels consisting of a one phase, hydrophilic system. Table 3.1 shows the main components of a partially hydrated hydrogel and the contribution that each component gives to the polymer matrix.

Component	Role
Unsaturated Hydrophilic Monomer	Forms the backbone of the three dimensional polymer matrix.
Glycerol	Acts as a humectant by reducing the rate of evaporation of water through hydrogen bonding.
Water	Plasticises the gel allowing it to conform to the site of attachment. Enhances permeability of actives through the matrix.
Initiator	Required to initiate polymerisation via the formation of active centres and donation of electrons (for radical polymerisation).
Cross linker	Bifunctional monomer/polymer gives the gel the ability to swell, without the loss of structural integrity (or 3D matrix).

Table 3.1 Components of partially hydrated monophasic hydrogels and their roles

The process used to convert the components listed in table 3.1 into a 3D polymer matrix is known as photopolymerisation. This involves the conversion of a photoinitator to free radical species. They react with the unsaturated bond on the hydrophilic monomer triggering a chain reaction known as propagation. Termination occurs when free radicals react together resulting in a polymer. Section 3.1 gives an in depth description of the stages of photopolymerisation.

3.4 Aims

The synthesis and mechanical testing of monophasic technology gels are essential to understand the properties possessed by sheet skin adhesive hydrogels. Extensive studies have previously been carried out in collaboration with First Water Limited. This chapter looks at the optimisation of conventional monophasic hydrogels, composed of NaAMPS, glycerol and water, giving scope to the development of new technologies for a range of dermal applications.

A series of formulations, composed of hydrophilic components should be investigated to determine the fundamental governing factors. Examining the influence of each component on the rheological and adhesive properties is essential. Manipulation of the three basic components in the system, NaAMPS, glycerol and water may provide information about adhesion and structural integrity of the gel.

Ostomy adhesives must possess a low level of swell, ensuring that they stay attached for the required length of time. NaAMPS has a high affinity for water and therefore a non ionic monomer should be incorporated into the formulation. Selection of a compatible unsaturated hydrophilic monomer which is UV polymerisable was investigated. The ease of coating the pregel solution before polymerisation is controlled by the viscosity. Therefore it is essential that it is modified by a suitable chemical.

The photoinitator and crosslinker mixture plays an important role within the pregel mixture. It initiates free radical polymerisation and aids the formation of the three dimensional polymer matrix respectively. The cohesive and adhesive strength of the gels should therefore be investigated to determine an optimum amount of Irgacure 184 and Ebacryl II.

Gels need to be synthesised for a range of applications e.g. for cosmetic or medical use. The type and time of application determines the strength of gel required. Ideally, the

adhesive strength should be controlled. If a suitable chemical added to the formulation brings about this change, this will reduce the time taken to produce tailor made gels.

The type of skin may also affect the adhesive properties of the gel, in particular greasy skin. Therefore, gels need to be composed with this in mind, to ensure that they can be attached to all types of skin.

Development of this type of technology should ultimately allow the incorporation of an array of water soluble active agents to be delivered topically. This will be discussed in a later chapter.

3.5 Procedure

A standard technique was used for the preparation of the monophasic pregels as shown in section 2.3.13. The photointiator - crosslinker mixture [Solution A] was placed into a sample vial and covered with a paper towel to eliminate stray light to ensure that the photoinitiator did not prematurely breakdown, to form free radicals. The mixture was placed on an IKA Vibrex VXR mechanical shaker, set at 100 revs/min for an hour, to ensure that the photoinitiator dissolved in the crosslinker forming a homogenous solution.

Hydrophilic monomer(s), glycerol and water (if required) [Solution B] where placed into a separate sample vial. The mixture was placed on the IKA Vibrex VXR mechanical shaker, set at 100 revs/min for twenty minutes, to allow all of the components to mix. Solution A was added to Solution B and the sample vial was covered with a paper towel, to prevent premature polymerisation. The pregel was placed on the mechanical shaker to ensure a homogenous solution was obtained.

The UV dryer Lab-MD1 provided the correct wavelength of light required to convert the photoinitiator into corresponding free radicals. Small aluminium trays were lined with silicone coated release paper (non coated side was face up in the tray). The pregel mixture was poured into the tray and moved gently to ensure that it formed an even coating. The tray was placed on the conveyer belt and passed twice under the UV lamp. The hydrogels were allowed to cool for ten minutes before being covered with the silicone coated release paper. The coated side was in contact with the top of the gel. The samples were then stored in resealable plastic bags until required.

3.6 Results

3.6.1 NaAMPS skin adhesive hydrogels

Extensive studies have previously been carried out to investigate the properties of NaAMPS skin adhesive (Flemming, 1999). They highlighted that a change in the formulation affects the adhesive and cohesive properties of the gel. Table 3.2 shows the formulations used to synthesise monophasic gels which highlights that if the monomer, glycerol or water ratios are varied, the rheological and adhesive properties can be altered. This allows gels to be tailor-made for a desired application.

Code	NaAMPS (% w/w)	G (% w/w)	H_20 (% w/w)	Description of the hydrogel
NA1	40.0	30.0	30.0	Transparent gel
NA2	43.0	26.0	31.0	Transparent gel
NA3	45.0	22.0	33.0	Transparent gel
NA4	50.0	14.0	36.0	Transparent gel

Table 3.2 NaAMPS based monophasic hydrogel compositions

The compositions in table 3.2 range from 40-50 % w/w monomer with varying amounts of glycerol. This has a dual role as a humectant and plasticiser. 0.20% w/w of a 3:10 ratio of Irgacure 184 (the photoinitiator) and Ebacryl II (the crosslinker) respectively, were added to each pregel composition. The results show that gels can be synthesised using various formulations. However, in order to achieve the desired properties, good adhesive and cohesive properties, the ratios of the components need to be altered depending upon the application. Peel strength results yield a relative cohesive strength

value of the hydrogel which can be used to assess the integrity of the gel, in conjunction with the strength of the adhesive bond between the hydrogel and substrate. The adhesive bond formed between NA4 or NA1 with the substrate was higher than that of NA2 or NA3. A typical peel strength for a NaAMPS gel using a smooth stainless steel substrate yields a force of approximately 10N/25mm. The results in figure 3.7 show that all have peel strengths below this value. The gels are not unusable since this will depend upon the application.

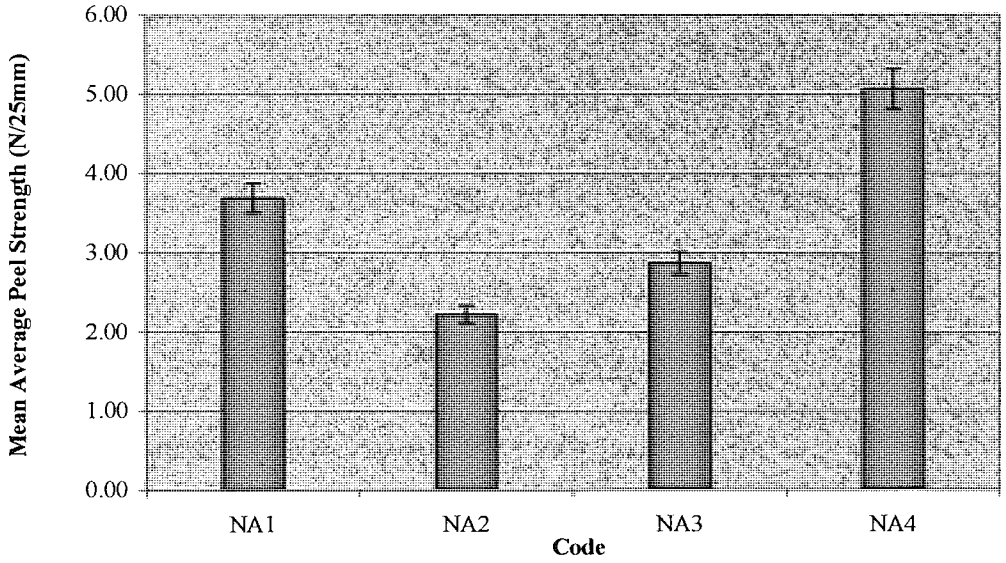


Figure 3.7 Peel strengths of monophasic hydrogels

Rheological studies of these gels showed that the elastic moduli (G') were higher than the viscous moduli (G''), a perquisite of viscoelastic skin adhesive hydrogels. Taking into consideration the ratio of monomer to the total ratio of glycerol to water, it shows that each component has a role to play. This indicates that a balance between the total monomer content and the plasticising agents need to be achieved for a cohesive gel. The viscoelastic behaviour was measured at a low frequency of 1 Hz and a high frequency of 10Hz to represent the application and removal of the skin adhesive respectively as shown in figure 3.8 and 3.9. To apply a gel, a reduced viscous component is required which allows the ease of attachment. Removal of the gel must take place cleanly without leaving a residue i.e. coming away intact from the substrate. NA2 has elastic and viscous moduli that are very similar at low and high frequencies and does not perform as well as the other

gels. NA4 has a dominant elastic modulus when compared to the viscous modulus at both low and high frequencies. Tan δ values below 1 indicate that the gel would not fail to the high frequency stresses which result in the loss of structural integrity.

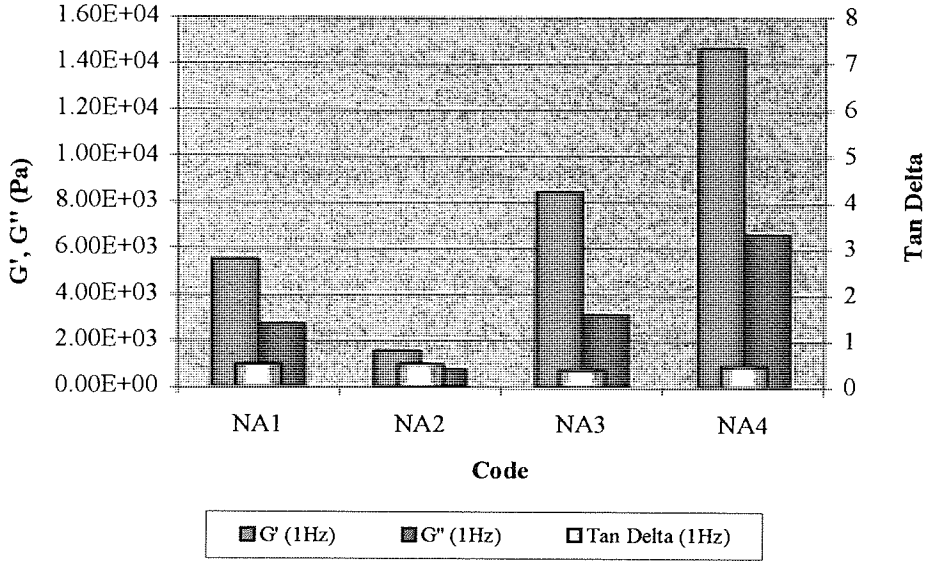


Figure 3.8 Rheological properties of NaAMPS hydrogels at 1 Hz

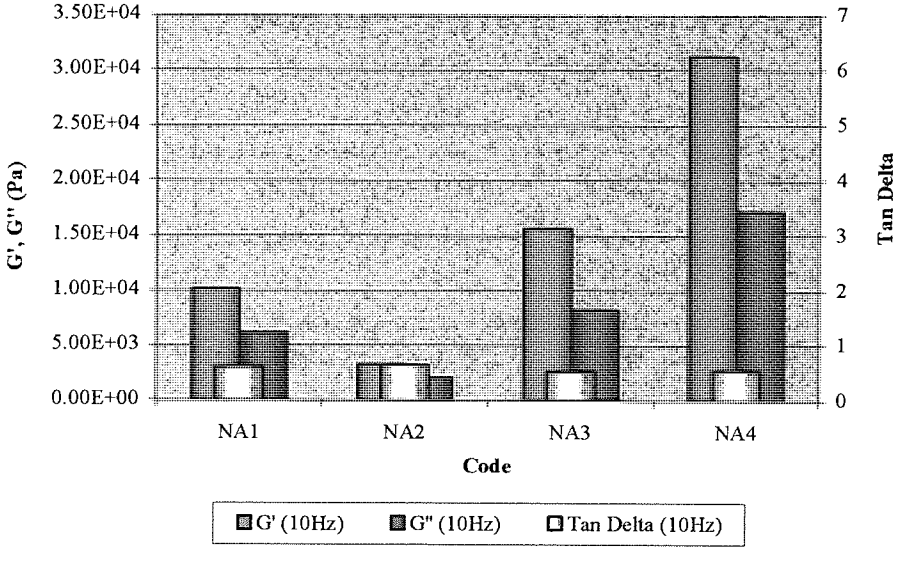


Figure 3.9 Rheological properties of NaAMPS hydrogels at 10 Hz

3.6.2 NaAMPS and NaAMPS - AMO skin adhesive hydrogels

Copolymers composed of NaAMPS an ionic monomer and AMO a non ionic monomer, were synthesised in accordance with the compositions shown in table 3.3. Corresponding hydrogels made up without the incorporation of the non ionic monomer AMO, were synthesised to compare the quality of these polymeric gels with those containing AMO and to establish its role within the polymer matrix. 0.20% w/w of a 3:10 ratio of Irgacure 184 (photoinitiator) and Ebacryl II (crosslinker) respectively were added to each pregel composition. Figure 3.10 illustrates the hydrogel peel strengths and highlights that the incorporation of AMO increases the force required to remove the hydrogel from the substrate. The 90° peel tests showed that these gels had approximately twice the peel strength of gels containing NaAMPS only. The incorporation of AMO yielded gels with good cohesive strength, which arises due to the increase of hydrogen bonding within the polymer matrix.

Code	NaAMPS (% w/w)	AMO (% w/w)	G (% w/w)	H_20 (% w/w)
NAH1	30.0	20.0	28.0	22.0
NAH2	38.0	0.0	35.0	27.0
NAH3	33.0	8.0	35.0	24.0
NAH4	35.0	0.0	38.0	27.0
NAH5	29.0	12.0	35.0	24.0
NAH6	33.0	0.0	40.0	27.0
NAH7	25.0	16.0	35.0	24.0
NAH8	30.0	0.0	42.0	28.0

Table 3.3 NaAMPS - AMO skin adhesive hydrogel compositions

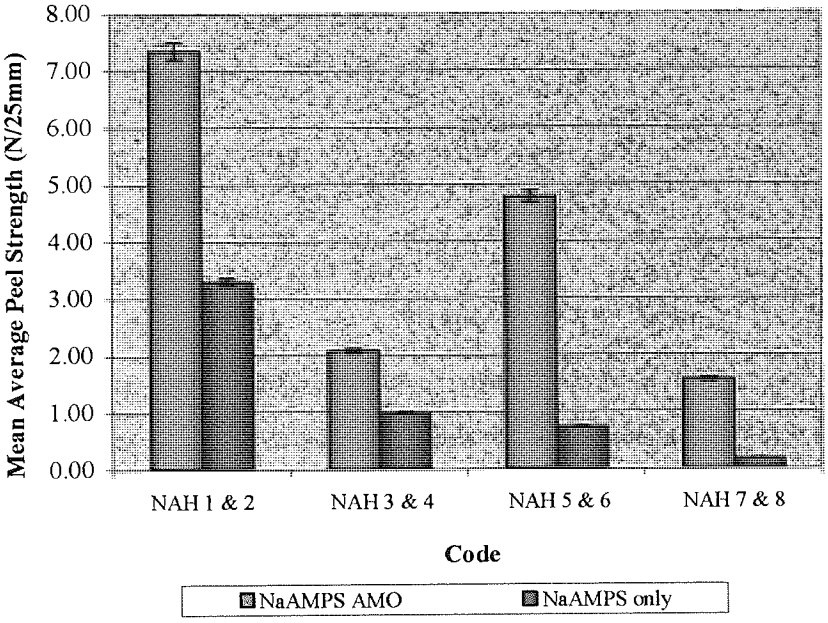


Figure 3.10 Peel strengths of copolymers of NaAMPS and AMO gels and homopolymers of NaAMPS

AMO has three potential sites where hydrogen bonding can occur. Figure 3.11 displays the hydrogen bonding between the amide group hydrogen on NaAMPS and the non ionic monomer. Poly NaAMPS and Poly AMO can hydrogen bond, allowing interchain linkages between the chains. This promotes the strength of the three dimensional polymer matrix, resulting in more cohesive gels. AMO has the ability to hydrogen bond with the glycerol and water which contributes and promotes structural integrity.

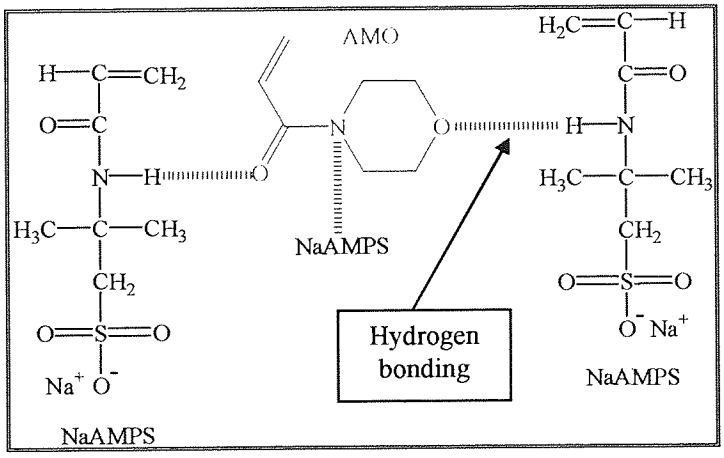


Figure 3.11 Hydrogen bonding of AMO with NaAMPS

3.6.3 NaAMPS gels with adhesion enhancing chemicals

The application and duration a hydrogel needs to stay in contact with skin, dictates if a low (below 10 N/25mm) or high peel strength (above 10N/25mm) is required. As shown in section 3.6.2 addition of a monomer which possesses the ability to hydrogen bond, is advantageous. The cohesive strength of a simple NaAMPS homopolymer can be increased by the addition of acrylic acid. 0.20% w/w at a 3:10 ratio of Irgacure 184 and Ebacryl II respectively, were added to each pregel composition. The NaAMPS gel without acrylic acid, gave the lowest peel strength. It was less cohesive than the other gels. Addition of 4% w/w resulted in the increase in the strength of the adhesive bond increasing, with considerable improvement in the cohesive properties.

NaAMPS (% w/w)	**G (% w/w)**	**H_20 (% w/w)**	**Acrylic acid (% w/w)**	**Description of the gel**
41.0	29.0	30.0	0.0	Transparent gel
41.0	29.0	30.0	4.0	Transparent gel, good adhesive strength
41.0	29.0	30.0	6.0	Transparent gel, good adhesive strength
41.0	29.0	30.0	8.0	Transparent gel, good adhesive strength
41.0	29.0	30.0	10.0	Transparent gel, good adhesive strength

Table 3.4 Compositions of NaAMPS homopolymers with increasing ratio of acrylic acid

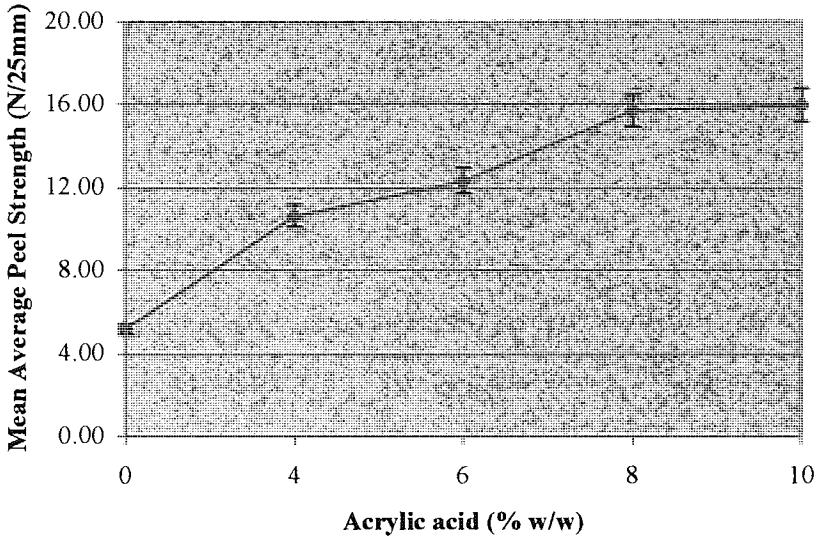


Figure 3.12 Peel strength of NaAMPS gels containing increasing amounts of acrylic acid

By varying the amount of the acrylic acid, the adhesive and cohesive strength can be controlled, thereby reducing the vast number of compositions that would need to be investigated. Acrylic acid has the potential to increase water binding and can remove the interfacial layer of moisture, holding it within the gel. An increase in the quantity of the adhesion enhancer produces higher peel strength gels.

The sodium ion associated with the NaAMPS has the potential to form the corresponding salt of acrylic acid, rendering it more water soluble. However, it does not possess a sulfonate group and is less hydrophilic compared to NaAMPS, resulting in a reduction in swelling.

3.6.4 Investigating the effects of varying the quantity of PI /XL

Adding an adequate amount of photinitiator to a pregel is essential. Free radicals are formed in the presence of the appropriate wavelength of light. This allowed adequate initiation and propagation of the monomer units. This section highlights the importance of incorporating an adequate amount of photoinitiator and crosslinker. A PI/XL mixture of Irgacure 184/Ebacryl II at a 3:10 ratio was added to the pregel formulations as shown

in table 3.5. Peel tests were conducted using the method stated in section 2.3.2.2. The incorporation of 0.05 or 0.10% w/w PI/XL to the composition resulted in leggy gels and they left a residue behind on the peel test substrate. This highlighted the poor cohesive properties of the gels. A lack of structural integrity arose with low levels of initiator and crosslinker producing a more viscous gel. The gel containing 0.30 % w/w of PI/XL was not as flexible as the gel containing 0.20 % w/w of the PI/XL mixture showing that the extra quantity of the crosslinker is restrictive and does not allow adequate chain rotation to occur. The gel was unable to conform to the uneven areas of attachment for example a human arm.

NaAMPS (% w/w)	AMO (% w/w)	G (% w/w)	H_20 (% w/w)	PI/XL (% w/w)
22.2	26.0	35.7	16.1	0.05
22.2	26.0	35.7	16.1	0.10
22.2	26.0	35.7	16.1	0.20
22.2	26.0	35.7	16.1	0.30

Table 3.5 NaAMPS – AMO compositions containing varying amounts of Irgacure 184/ Ebacryl II

Addition of a crosslinking agent ensures that the polymer did not dissolve in solvents. Motions of the polymer chains were restricted. In hydrogels a three dimensional polymer matrix is achieved through covalent crosslinking by adding a bifunctional monomer.

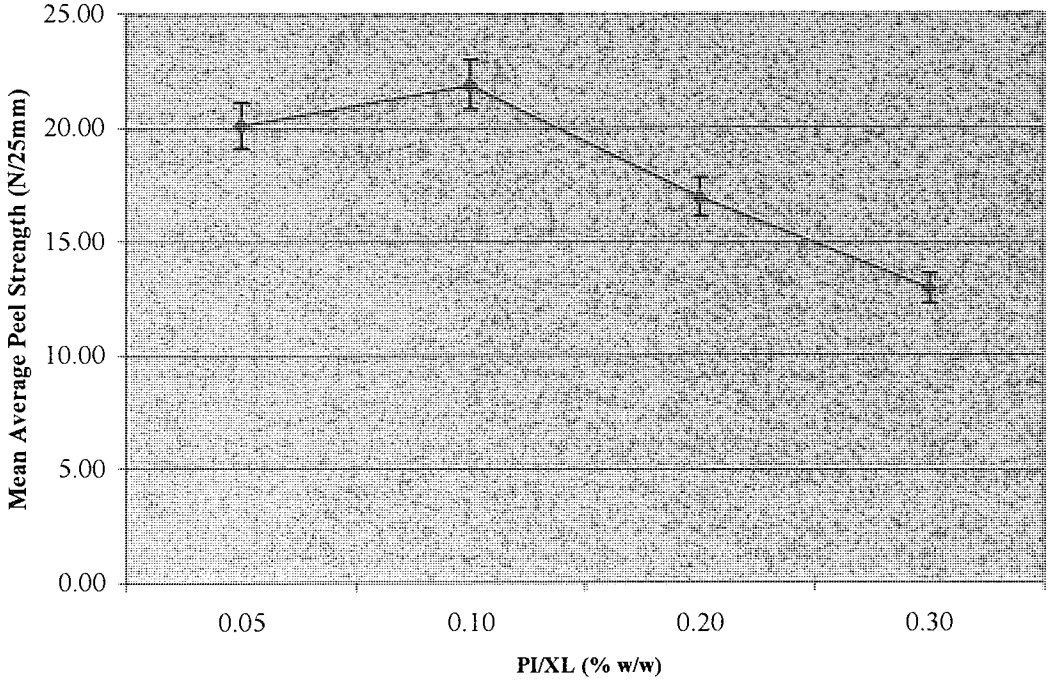


Figure 3.13 Peel strength of monophasic skin adhesive hydrogel containing varying amounts of PI/XL at a 3:10 ratio

3.6.5 Investigating the effects of varying the ratio of PI to XL

In the previous section it was shown that the optimum amount of the PI/XL mixture was 0.20 % w/w to produce a gel with the desired viscoelastic properties. This section looks at how varying the ratio of photoinitiator to crosslinker affects the properties of a skin adhesive hydrogel, when the total amount of PI/XL was kept static at 0.20% w/w. Low quantities of initiator were present in the 1:10 and 2:10 PI/XL solutions. These gels left residues on the peel test substrate, showing poor cohesive strength. An optimum amount of initiator must be added to ensure that there are enough free radicals produced when exposed to UV light. The vinyl groups of the monomers and crosslinker react with the radicals. Reactions between these active species result in the formation a three dimensional polymer matrix. An optimum amount of crosslinker is required to ensure that the cohesive strength is acceptable, with no residuals on the surface after removal. Low

peel strengths in this instance show that the matrix had not formed. Residual monomers were present due to the combination of low levels of initiator and crosslinker.

NaAMPS (% w/w)	AMO (% w/w)	G (% w/w)	H_20 (% w/w)	PI/XL ratios
22.2	26.0	35.7	16.1	1:10
22.2	26.0	35.7	16.1	2:10
22.2	26.0	35.7	16.1	3:10
22.2	26.0	35.7	16.1	4:10

Table 3.6 NaAMPS – AMO compositions with varying ratios of Irgacure 184/Ebacryl II

The objective of this investigation was to determine the optimum ratio of PI/XL. The results highlighted that 0.20% w/w at a 3:10 ratio of PI/XL gave optimum results.

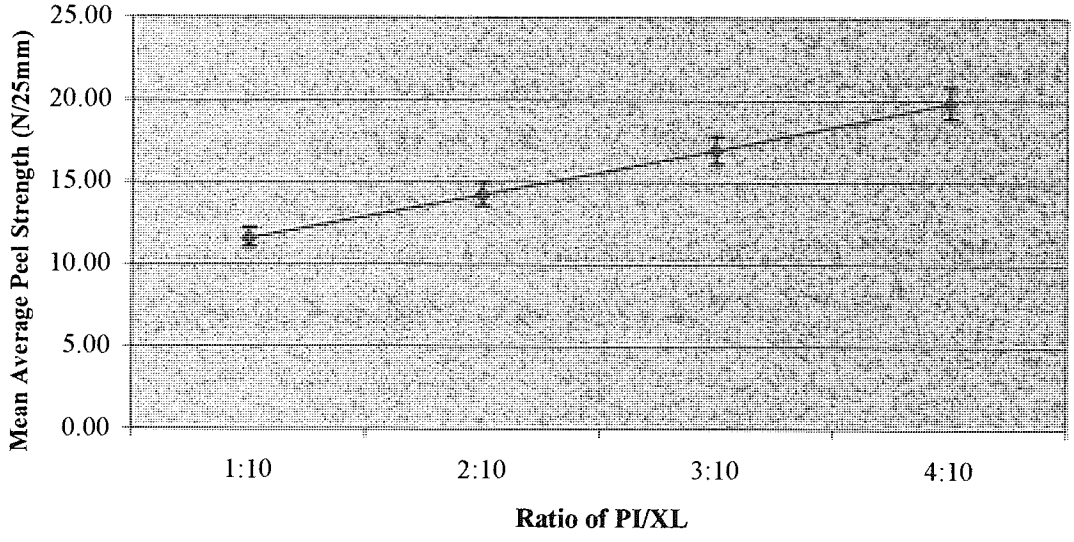


Figure 3.14 Peel strengths of monophasic skin adhesive hydrogel at varying ratios of PI to XL

3.6.6 Monophasic gel compositions compatible with greasy skin

Skin adhesives hydrogels are generally synthesised without taking into account the levels of oil (sebum) produced by certain individuals. This is often much higher than those with normal skin. The oil interferes with the adhesive bond between the gel and skin. This section focuses on monophasic gels tailor-made for individuals with greasy skin. A normal monophasic gel does not have the ability to remove a substantial amount of interfacial oil. The composition can be modified to incorporate a surfactant which has the ability of drawing some of the excess oil and encapsulating it within the surfactant, resulting in the formation of a good adhesive bond.

Block surfactants P65 and L64 were incorporated into the formulations as shown in table 3.7. These surfactants consist of blocks of polyethylene oxide and polypropylene oxide and despite both surfactants having a similar hydrophile-lipophile balance, with a range of 12-18, they performed in different ways. The polymeric surfactant P65 (approximate molecular weight 3400) has a hydrophobic component with an approximate molecular weight of 1800 and the hydrophilic component represents approximately 50 % of the molecule by weight. L64 has an approximate molecular weight of 2900 with a hydrophobe molecular weight of approximately 1800 and the hydrophile represents 40 % of the molecule by weight.

Both gels have the potential to remove excess oil, however, the actual environment into which they were placed also affects their role. They possess equivalent amounts of polypropylene oxide and the only difference is the amount of hydrophilic material present. P65 is more hydrophilic than L64, which results in the monomer interacting with the components of the gel formulation, increasing compatibility.

NaAMPS (% w/w)	AMO (% w/w)	G (% w/w)	H_20 (% w/w)	P65 (% w/w)	L64 (% w/w)
22.2	26.0	35.7	16.1	0.0	0.0
22.2	26.0	35.7	16.1	0.1	0.0
22.2	26.0	35.7	16.1	0.5	0.0
22.2	26.0	35.7	16.1	1.0	0.0
22.2	26.0	35.7	16.1	1.5	0.0
22.2	26.0	35.7	16.1	0.0	0.1
22.2	26.0	35.7	16.1	0.0	0.5
22.2	26.0	35.7	16.1	0.0	1.0
22.2	26.0	35.7	16.1	0.0	1.5

Table 3.7 Compositions of monophasic gels containing surfactants to allow the use of the gels on greasy skin

The gels containing no surfactant possess higher peel strengths than those containing surfactant. This indicates that the incorporation of a hydrophilic – hydrophobic agent of high molecular weight lowers the peel strength. The addition of a polymeric surfactant causes a restriction in the molecular motion by reducing the free space. An increase in the hydrophobic content as shown by adding varying amounts of L64, results in a decrease in peel strength. Gels containing P65 have higher peel strengths than those containing the block surfactant L64.

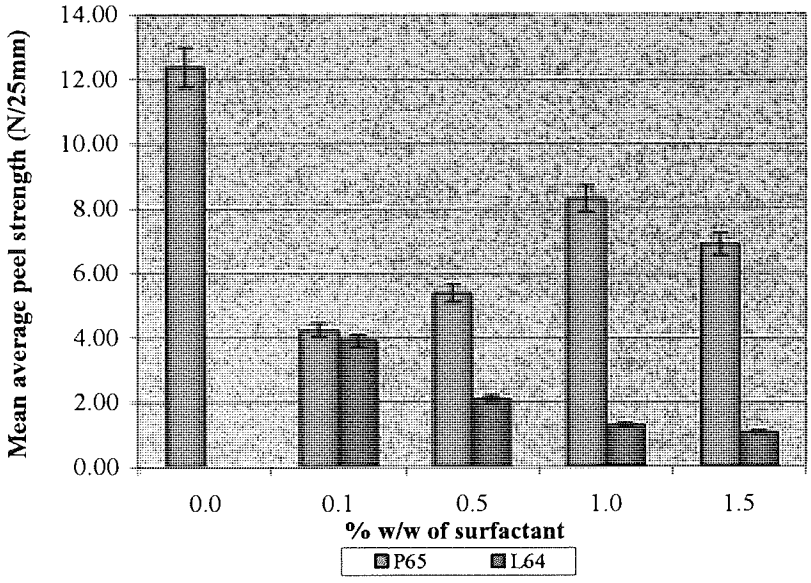


Figure 3.15 Mean average peel strengths of gels containing surfactants

Rheological studies highlighted that gels containing 0.1 or 0.5 % w/w P65 had similar elastic and viscous moduli at low and high frequency, compared to the gel containing no surfactant. The addition of 1% w/w P65 resulted in higher values of elastic and viscous moduli with the gels maintaining their structural integrity at high frequency stress (10 Hz). Also, when removed it did not leave a residue. Tan δ values were less than 1 showing that the elastic moduli were dominant compared to the viscous moduli. A gel containing more than 1 % w/w of P65 could be applied to very oily skin. However, the difference between the elastic and viscous moduli is not as much when compared to the other gels. For compositions containing less than 1% of w/w surfactant, the viscous modulus is lowered. The ideal gel contains 1.0 % w/w of P65. High levels of surfactant will irritate the skin. Therefore, a gel containing a minimum amount of surfactant which results in maximum impact (removal of the oil allowing attachment) is highly desirable.

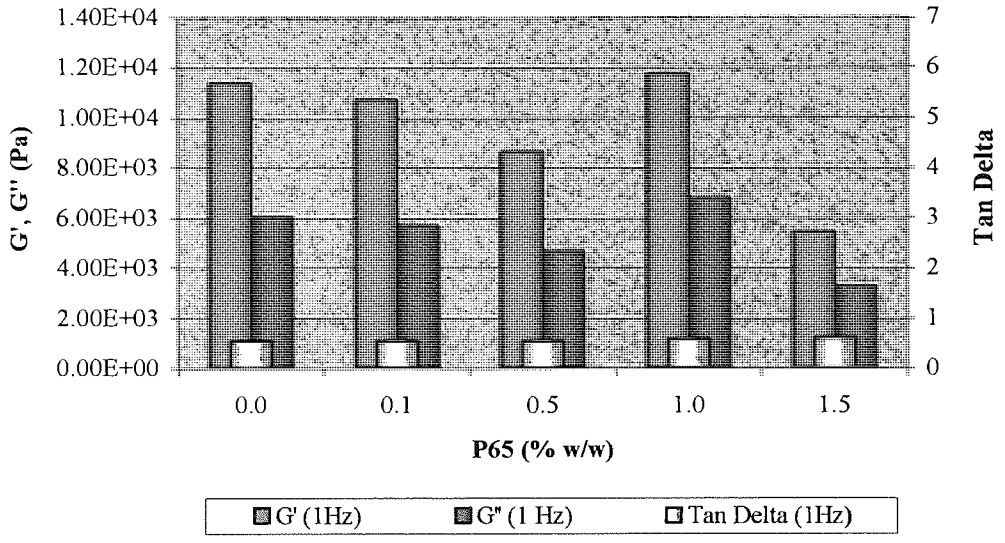


Figure 3.16 Rheological behaviour of compositions with varying amounts of P65 at 1 Hz

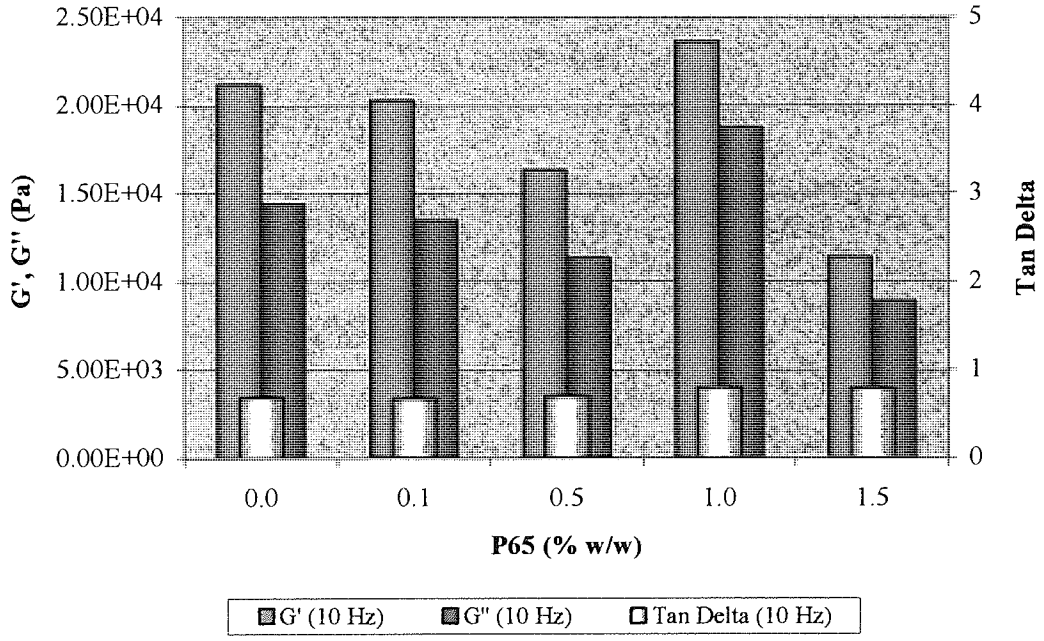


Figure 3.17 Rheological behaviour of compositions with varying amounts of P65 at 10Hz

The gels containing L64 yielded higher values of elastic and viscous moduli at low frequency stresses showing that they can be attached, but not with similar ease to those gels containing no surfactant. Gels containing L64 had a higher viscous component compared to those containing P65. Incorporation of this surfactant affected the viscosity

of the pregel more than P65. A high hydrophobic content results in the restriction and coiling of the surfactant, minimising interactions with the aqueous environment. This reduces the mobility of the polymer leaving a minimal number of ethylene oxide sites to interact with the water.

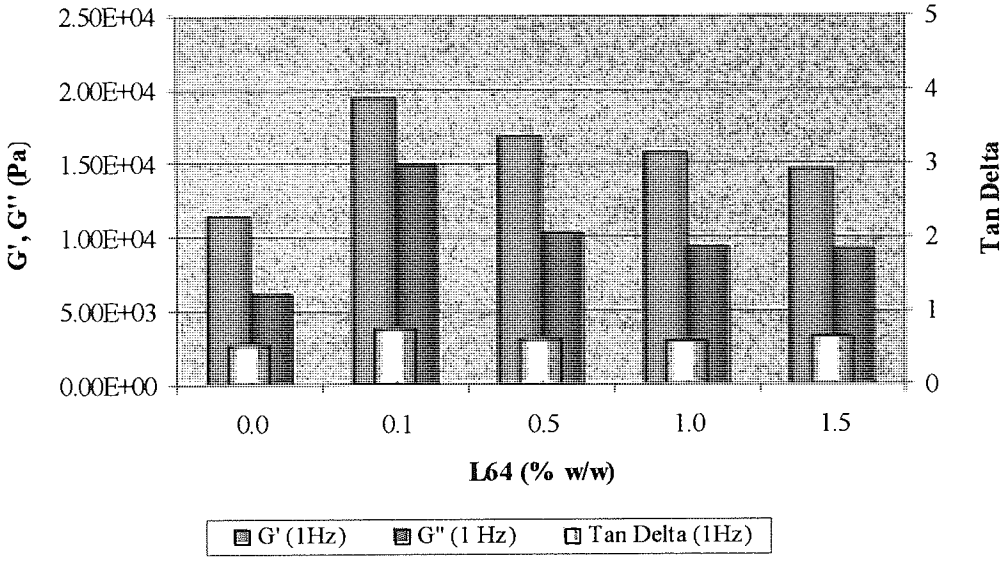


Figure 3.18 Rheological behaviour of compositions with varying amounts of L64 at 1 Hz

Figure 3.19 shows the rheological behaviour of various combinations, containing different quantities of L64 subjected to a higher shear frequency 10 Hz. The gel containing 0.1 % w/w of L64 had a higher viscous modulus than elastic modulus showing that it behaved more like a fluid. Upon removal, the gel did not come away in one piece and left residue on the area of attachment. Increasing the amount of L64 resulted in higher elastic and viscous moduli compared to the gel containing 0 % w/w of surfactant, at 10 Hz, showing that the structural integrity had been altered considerably and was not as functional as the gels containing P65.

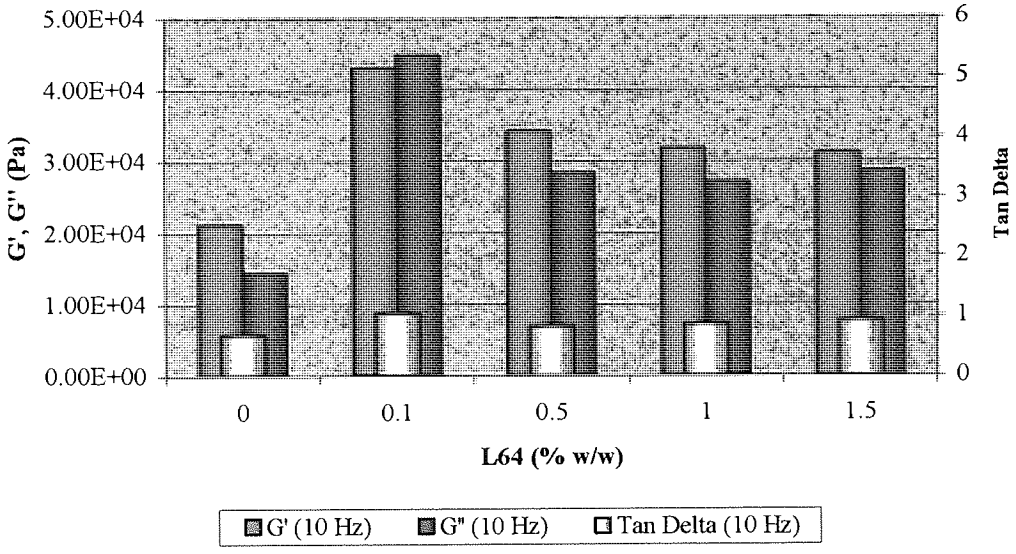


Figure 3.19 Rheological behaviour of compositions with varying amounts of L64 at 10Hz

Preliminary tests were carried out to investigate if these gels could potentially be applied to greasy skin. Nivea cream was applied to the forearm and resulted in the elevation of the level of oil on the skin, causing temporary greasiness. Two centimetre squared samples were cut from all of the compositions shown in table 3.7. They were placed onto the skin and the time of attachment was monitored.

As anticipated the gel with no surfactant did not adhere to the greasy skin and unexpectedly gels containing L64 did not adhere. However, the gels containing P65 stayed in contact with the greasy skin for two hours. Comparing P65 and L64, the latter has a shorter chain length with elevated levels of hydrophobicity. Therefore interaction with the hydrophilic matrix is limited and this affects its ability to encapsulate the oil within the gel. P65 is more hydrophilic and has the ability to interact with its environment allowing excess oil to be removed from the skin and encapsulated within the gel. If a monophasic gel were to be synthesised specifically for attachment to greasy skin 1% w/w of P65 would be optimum, providing an acceptable peel strength and good rheological properties.

3.6.7 Synthesis of AMO based skin adhesive hydrogels

Gels containing ionic monomers for example NaAMPS have a high affinity for water and are not suitable if they come into contact with large quantities of moisture. Skin adhesive hydrogels are partially hydrated and have the ability to absorb and retain limited amounts of moisture. This ultimately resulted in the loss of adhesion. The gels in this section are composed for a specific application, which utilises them as an adhesive, attaching an ostomy device to the skin. Ostomy adhesives come into contact with a surgically made opening in the abdomen wall known as the stoma. Extrudate is removed from the small intestine of a human body through the opening. Therefore, a NaAMPS based gel will not stay attached for long periods of time and will result in detachment of the device

Code	**AMO (% w/w)**	**G (% w/w)**	**H_20 (% w/w)**	**Description of the hydrogel**
AH1	70.0	20.0	10.0	Low cohesive strength
AH2	60.0	20.0	20.0	Transparent gel, low cohesive strength
AH3	56.0	28.0	16.0	Transparent gel, excellent adhesive and cohesive strength
AH4	50.0	30.0	20.0	Transparent cohesive gel, low adhesive strength
AH5	50.0	20.0	30.0	Transparent cohesive gel, low adhesive strength
AH6	45.0	30.0	25.0	Transparent gel, cohesive and adhesive strength

Table 3.8 Compositions of hydrogels based on the non ionic monomer AMO

AMO, a non ionic monomer, has a lower affinity for water compared to an ionic monomer, resulting in the lower degree of swell. Extensive swelling of a gel will ultimately result in the loss of structural integrity, leading to the deterioration of its mechanical properties. The gel becomes brittle and cannot fulfill its role resulting in the device detaching. These gels were designed specifically to have low swell and with the potential to be used as alternatives to conventional ostomy adhesives, allowing other components to be incorporated within this three dimensional polymer matrix.

The gels composed of 50 % w/w AMO, 30% w/w glycerol and 20% w/w water yielded cohesive gels with low peel strengths. These would be ideal for ostomy adhesives because they need to be reapplied with minimal trauma to the skin. From a synthetic perspective the viscosity of these gels were not at an acceptable level, causing problems when they were coated onto the release paper. The next section addresses this problem by incorporation of a viscosity modifier into the gels.

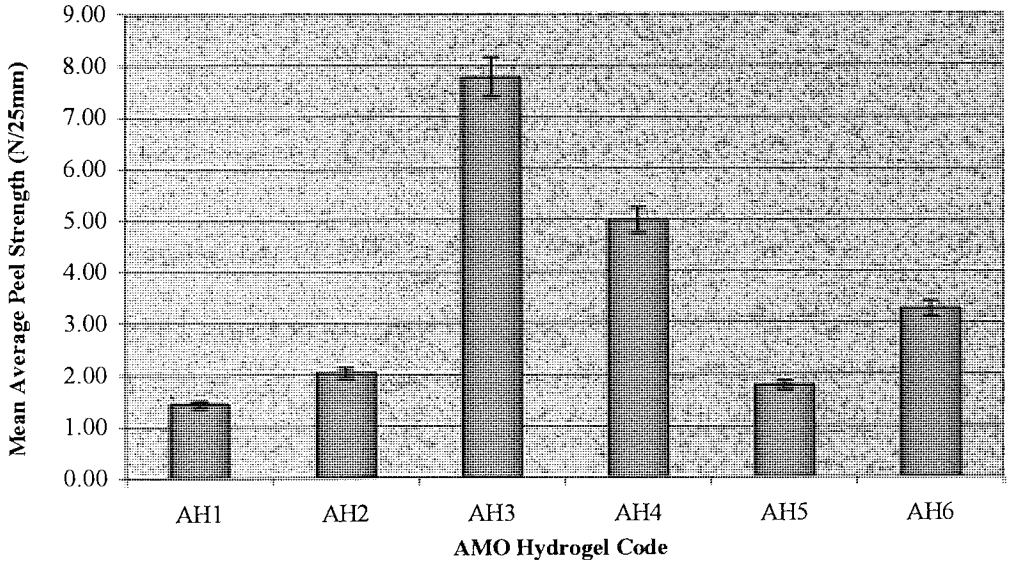


Figure 3.20 Mean average peel strengths of AMO based skin adhesive hydrogels

3.6.8 Incorporation of a viscosity modifier to increase the viscosity of the AMO composition

AMO based skin adhesive hydrogels as made in section 3.6.7 were less viscous than the NaAMPS – AMO pregel compositions. The viscosity was increased by adding a polyquaternium polymer known as PQ4. This cationic polymer was added in very small quantities as shown in table 3.9. Incorporation of over 0.4 % w/w resulted in the pregel becoming highly viscous and the mixture could not be polymerised. The mobility of the free radicals, the unsaturated monomers and crosslinker would be restricted. This reduced the opportunity of forming a three dimensional polymer matrix.

AMO (% w/w)	**Glycerol (% w/w)**	**H_2O (% w/w)**	**PQ4 (% w/w)**	**Description**
56.0	28.0	16.0	0.2	Transparent cohesive gel
56.0	28.0	16.0	0.3	Transparent cohesive gel
56.0	28.0	16.0	0.4	Transparent cohesive gel

Table 3.9 Compositions of AMO hydrogels containing PQ4 as a viscosity modifier

The gels formed were transparent clear gels with a good cohesive strength. Peel strengths as shown in figure 3.21 increased when compared to the composition without the PQ4 sample AH3 in section 3.6.7. PQ4 has functional groups present within the polymer chain, which can hydrogen bond with AMO, increasing the cohesive strength. Hydrogen bonding between water or glycerol with PQ4 can also occur. This contributes to the cohesive strength. Another advantage to using a cationic polymer is that it will have a lower affinity for water compared to NaAMPS and is suited for the application as an ostomy adhesive.

This type of gel is not exclusively applicable as an ostomy adhesive, it can be used for other applications. However, NaAMPS homopolymers and some NaAMPS – AMO copolymers cannot be used to attach ostomy devices due to the high level of swell of these gels. As shown in figure 3.21 the peel strengths for a gel containing 0.2 or 0.3 % w/w were similar and the pregel viscosity increased with the increase in the amount of PQ4.

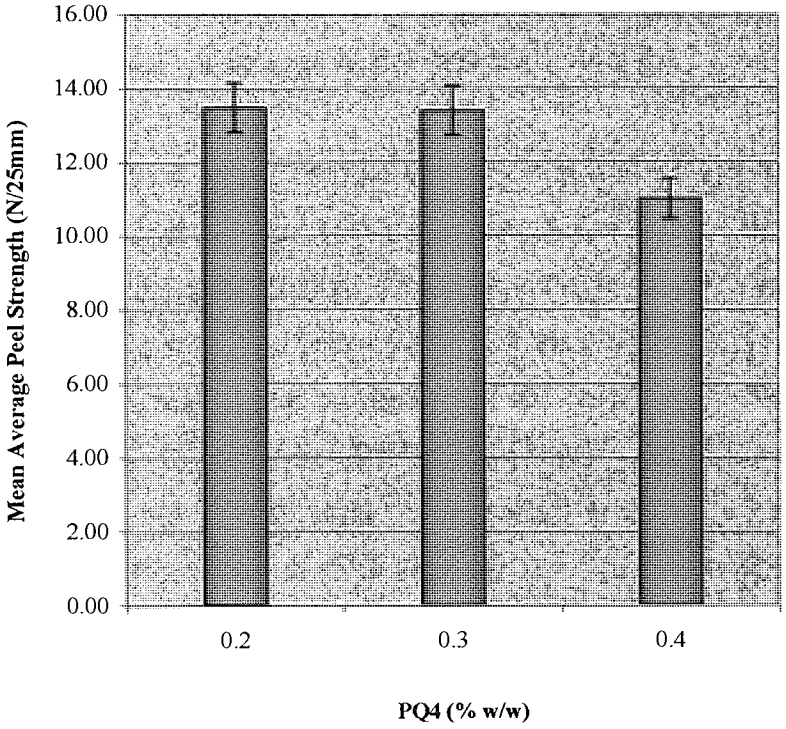


Figure 3.21 Peel strengths of AMO based hydrogels containing a viscosity modifier PQ4

From a synthetic point of view, the PQ4 was not added directly to all other components within the composition. This resulted in a heterogeneous pregel and was rectified by dissolving the PQ4 in water, before adding AMO and glycerol. 0.20 % w/w of Irgacure 184 and Ebacryl II were added to each composition at a 3:10 ratio respectively.

3.7 Discussion

This chapter highlights that conventional skin adhesives composed of NaAMPS, glycerol and water are not as versatile as one would expect. However, by introducing subtle changes in the composition, a gel can be altered to comply with new application requirements. The focus was placed on the adhesive, cohesive and mechanical behaviour, which showed that the underlying fundamentals must be comprehended before modifications can be implemented to the pregel formulation. The gels were synthesised for general skin application with the scope of allowing active agents to be delivered topically. Active agents were not selected at the start of this study.

The initiating and crosslinking systems consisted of Irgacure 184 a Norrish I type initiator and Ebacryl II a difunctional acrylate based polymer. An optimum ratio and quantity were selected from adequate peel strength data. The addition of the correct amount of initiator ensured that a good supply of primary free radicals were available. These species can react with the vinyl group on the monomer and the crosslinker which initiates the process of polymerisation. The addition of 0.05 % w/w of Irgacure 184/Ebacryl II at a 3:10 ratio resulted in a high peel strength gel as shown in figure 3.14, however, the physical integrity of the gel was unacceptable. The gel was leggy showing it would not be able to fulfil its application.

From a synthetic perspective, the lack of initiator resulted in the presence of residual monomer in the hydrogel. An adequate supply of free radicals does not result in the formation of a three dimensional polymer matrix unless Ebacryl II is present. This chemical has the ability to link monomer units together through covalent bonds. The structure synthesised will not dissolve when in contact with a solvent, instead it swells due to the presence of the crosslinks. When an excessive amount of crosslinker is incorporated into the formulation this changed the integrity of the gel. It became more rigid and could not conform to the contours of the skin. The reduction in elasticity will inherently cause implications if the gel were used as a dermal delivery device for active agents.

The basic NaAMPS homopolymeric gels were modified to incorporate a non ionic monomer AMO. The corresponding copolymers displayed improved cohesive and adhesive properties. The compositions displayed in table 3.3 highlight this trend and peel strengths are approximately twice that of the corresponding NaAMPS gels. AMO has three potential sites for hydrogen bonding as shown in figure 3.11. The gels formed possess high cohesive strength due to interactions with NaAMPS. The orientation of the polymer chain may allow the amide hydrogen to interact with the sites on AMO. The interaction with the glycerol and water contribute to the structural integrity of the gel.

Skin type can have a dramatic effect on the adhesive bond formed between monophasic gels, in particular greasy skin. Monophasic gels do not adhere to greasy skin as shown in section 3.6.6. The pregel formulations were modified to incorporate non ionic surfactants P65 and L64. The potential of these surfactants to remove excess oil from the surface of the skin were investigated. Encapsulation of the oil within the surfactant should enable the gel to adhere to the skin. The surfactants had the potential to encapsulate the oil, however, their surrounding environment played a major role. Surfactants' having similar HLB values do not guarantee that they will perform in the required manner. An increase in the hydrophobic component results in the restriction of molecular motion which contributes to the lower peel strength values. L64 has a higher hydrophobic content when compared to P65 yielding lower peel strengths as shown in figure 3.15.

The rheological studies of gels containing 0.1 and 0.5 % w/w of P65 presented similar mechanical properties elastic and viscous moduli at low and high stresses to the monophasic gel containing no surfactant. The addition of 1.0 % w/w resulted in higher values of elastic and viscous moduli. The orientation of the hydrophobic component of the surfactant differs. The hydrophobic groups, polypropylene oxide came into contact with the top surface of the gel. The elastic modulus was greater than the viscous modulus and the Tan δ value was less than 1 for the gels containing P65. High levels of surfactant are not ideal because the risk of developing a skin irritation increases. Ideally, less than 1 % w/w of surfactant results in the removal of the excess oil from the skin.

Gels containing L64 did not perform as well as those containing P65. The gels had similar elastic and viscous moduli at high shear stresses and low peel strengths. The removal of these gels left a residue behind and the structural integrity was not maintained. The lack of compatibility is accounted by the structure of the surfactant. It contains similar amounts of polypropylene oxide as found in P65. However, it had less hydrophilic content. This rendered it less compatible within the predominantly hydrophilic three dimensional polymer matrix. Preliminary tests were carried out on self imposed greasy skin, by placing Nivea cream onto the forearm. Samples containing the surfactant L64 highlighted that they did not have the ability to remove excess oil from the skin. This resulted in the gel not adhering to the skin. P65 containing gels encapsulated the excess oil and formed an adhesive bond between the skin and the gel. Gels remained on the skin for two hours and could be used to deliver topically.

For a specific application e.g. ostomy adhesive, the pregel formulation can be modified to accommodate the requirements. A non ionic polymer (poly AMO) was synthesised and possessed a lower affinity for water than poly NaAMPS, therefore it remains attached for a longer period of time. An ostomy device is attached to a surgically created opening in the abdomen. If moisture comes into contact with the gel, it will be absorbed. This gel can be used for skin that perspires excessively. The viscosity of the non ionic AMO based pregel was lower than the NaAMPS-AMO pregels. Poly quaternium 4 was added to increase the viscosity of the pregel allowing similar thickness gels to be synthesised. The addition of PQ4 (0.2-0.4% w/w) resulted in an increase in viscosity and the peel strength when compared to the gel containing no viscosity modifier. Interaction between the PQ4 and AMO is possible which accounts for the increase in the cohesive strength through hydrogen bonding.

Chapter 4

Biphasic Gel Technology

4.1 Introduction

4.1.1 Biphasic Technology

Biphasic technology is the term used to describe hydrogels consisting of a two phase system (one hydrophilic component and the other a hydrophobic component). The previous chapter looked at monophasic hydrogels. A limited number of hydrophilic active agents can be incorporated, dependent upon their solubility within the pregel. Table 4.1 shows the main components of a partially hydrated biphasic skin adhesive hydrogel and the contribution each component makes to the polymer matrix.

Component	Role
Unsaturated Hydrophilic Monomer	Forms the backbone of the three dimensional polymer matrix.
Unsaturated Hydrophobic Monomer	Allows the incorporation of hydrophobic active agents to be dissolved within this domain. They cannot be located within the hydrophilic domain.
Solvent bridging monomer	Links the hydrophilic and hydrophobic monomers together. It contributes to the properties of the gel.
Glycerol	Acts as a humectant by reducing the rate of evaporation of water through hydrogen bonding.
Water	Plasticises the gel allowing it to conform to the site of attachment. Enhances permeability of actives through the matrix.
Surfactant	Added to form micelles, by encapsulating the unsaturated hydrophobic monomer producing a homogeneous pregel.

Component	Role
Initiator	Required to initiate free radical polymerisation via the formation of active centres and donation of electrons.
Cross linker	Bifunctional monomer/polymer gives the gel the ability to swell without the loss of its structural integrity or three dimensional polymer matrix.

Table 4.1 Components of partially hydrated biphasic hydrogels and their roles

4.1.2 Hydrophobic Monomers

Hydrophobic monomers as shown in figure 4.1 are water insoluble chemicals possessing characteristic groups for example an alkane backbone structure which is composed of carbons and hydrogens, alkenic groups, aryl or silicone. This type of monomer is classed as non polar and offers resistance from polar solvents for example water.

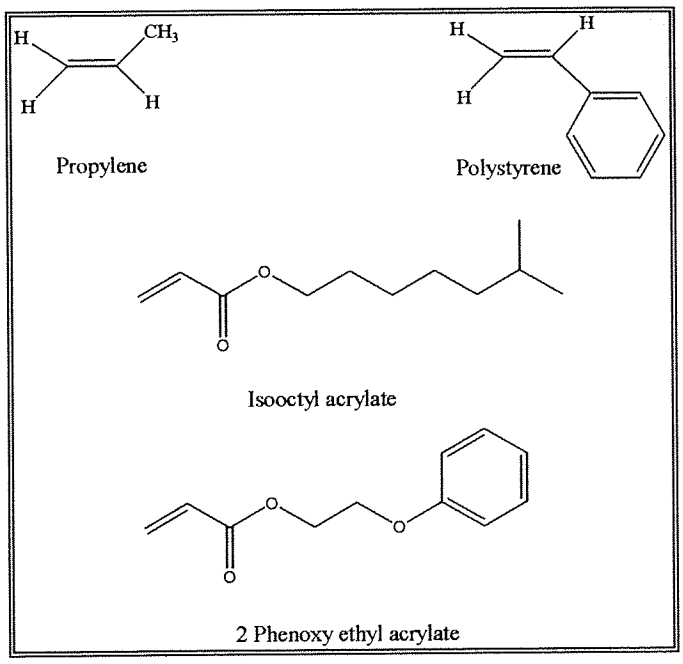


Figure 4.1 Chemical structures of hydrophobic monomers

Selection of a monofunctional hydrophobic monomer requires careful consideration, to ensure that it can be used in an adapted monophasic gel formulation. The monomers in figure 4.1 include vinyl or vinyl esters functional groups. The vinyl containing groups are more hydrophobic in comparison to those containing an ester component, which imparts less hydrophobicity. The incorporation of an aromatic group is not ideal, since this would not display the desired properties for a partially hydrated hydrogel. Monofunctional monomers based upon the acrylate series, would allow free radical polymerisation synthesis using UV technology. The size of the hydrophobic monomer is of importance. The formulation for monophasic gels would be modified to incorporate a highly hydrophobic monomer. Larger molecules will phase separate at a faster rate than their smaller counterparts. The addition of an unsaturated hydrophobic monomer to a hydrophilic pregel mixture will result in a heterogeneous solution. Incorporation of a suitable surfactant will aid its dispersion, resulting in a homogeneous solution.

4.2 General Classification of Surfactants

Surfactants are absorbed at the interface and have a molar mass in excess of 300. These types of species possess one common feature; they are amphipathic. The molecule consists of two parts, one which is the non polar hydrophobic portion (usually a straight or branched chain hydrocarbon containing 8-18 carbons) and the other being the polar hydrophilic portion as shown in figure 4.2. Surfactants are classified in accordance to the nature of the hydrophilic head group. They aid the distribution of a hydrophobic component within a hydrophilic component or vice versa depending upon the type of surfactant added (Tardos T.F, 2005, Farn R., 2006).

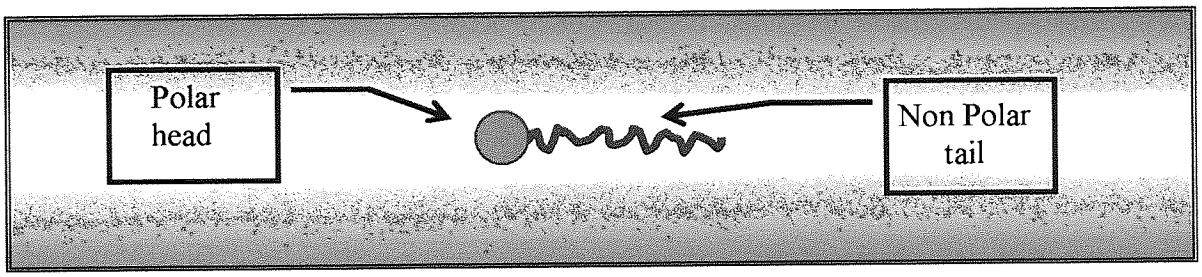


Figure 4.2 Schematic illustration of a surfactant molecule

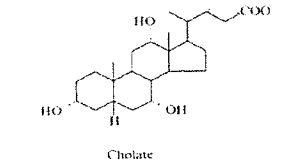
In an aqueous environment the interactions between a non polar tail and water molecules are weak whereas polar head groups become associated with water molecules via dipole interactions. The strong interaction with water renders the surfactant soluble. The role of the surfactant is to reduce the surface tension between two immiscible phases by adsorbing at the interface lowering the free energy at the phase boundary.

4.2.1 Naturally occurring biosurfactants and synthetic surfactants

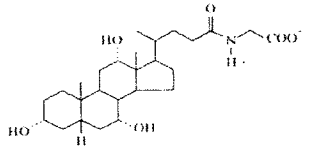
Polar lipids found in all living organisms are referred to as nature's surfactants (also known as biosurfactants). They are used in systems to overcome solubility problems, as emulsifiers or as dispersants and modify surfaces. Bile salts (e.g. cholate or glycocholate conjugation of glycine with cholate as shown in figure 4.3) are produced in the gall

bladder, situated in the liver. They are extremely efficient at solubilising fat components found in blood. The phospholipids pack in ordered bilayers forming the cell membrane structure which ranges from 6 to 10nm in thickness.

Phospholipids located in the cell membrane, possess both hydrophilic and hydrophobic components. As shown in figure 4.4 they form closed bimolecular sheets in aqueous solution and provide a barrier to the movement of polar components from both the outer and inner sides of the cell. Membrane proteins function as a gate, pump, receptor, energy transducer, cell recognition protein and catalytic enzyme. They are located on the inside, outside or the span of the membrane, depending upon their function. Membranes are asymmetric and the inside surface differs from the outside.



Cholate



Glycocholate

Figure 4.3 Bile salts

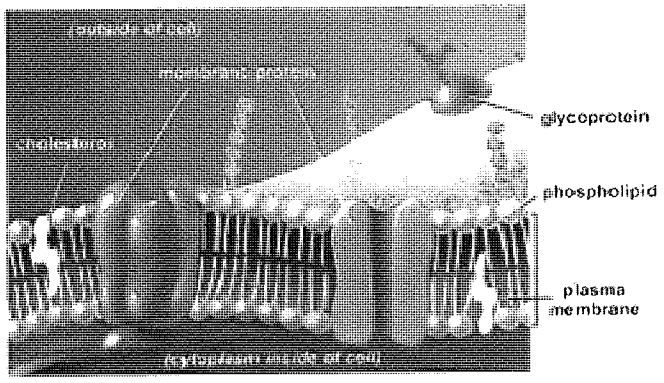


Figure 4.4 Fluid mosaic model

These fluid structures allow the rapid diffusion of proteins and phospholipids along the membrane surface. A single phospholipid molecule could travel across the cell in a few seconds. Lipid molecules can potentially exchange with neighbours over a million times per second. Fluidity is controlled by the cells and protein mobility. It is altered by the addition or withdrawal of molecules e.g. cholesterol or unsaturated fatty acids into the membrane structure. An increase in fluidity results in the disruption of these molecules.

The process of breathing results in the repeated cycle of expansion and contraction of mammalian lungs. Lattices of alveoli (figure 4.5) are bubble-like structures, joined together. The lung provides an enormous surface area for gas exchange. The surfaces of the alveoli are coated with a mixture of lipids and proteins known as lung surfactant. They lower the surface tension at the alveolar surface allowing the expansion and prevent it from collapsing. The surfactants prevent water droplets from blocking the airways. Lung surfactant consists of dipalmitoyl phosphatidylcholine (DPPC) a phospholipid, other phospholipids, proteins (SP-A, B, C, and D) and cholesterols (neutral lipids) and trace amounts of other substances (Haagsman H.P., 2001).

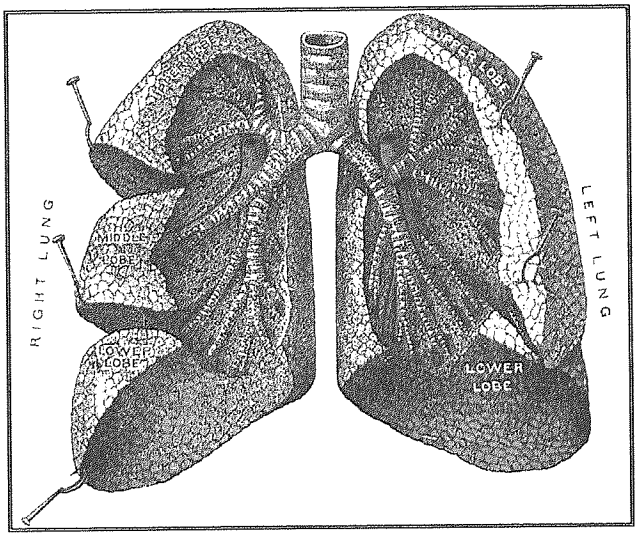
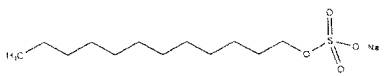
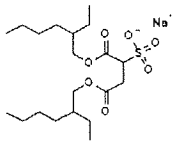
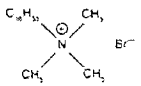
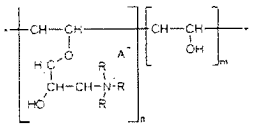
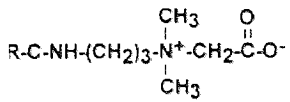
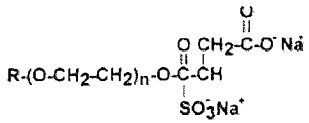
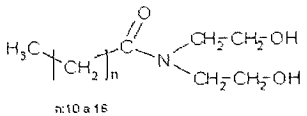
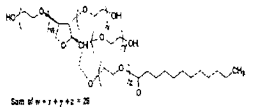


Figure 4.5 Human Lungs

Naturally occurring surfactants are highly selective and expensive compared to synthetic ones. Synthetic surfactants are classed into four groups anionic, cationic, amphoteric and non ionic. Table 4.2 illustrates a few of these surfactants and their applications.

Type of surfactant	Examples		Application
Anionic	 Sodium lauryl sulfate (SLS)	 Aerosol OT Sodium di(2ethylhexyl)sulfosuccinate	Detergent, emulsifying, solubilising and wetting agent
Cationic	 Cetyl trimethyl ammonium bromide (CTAB)	 Quaternium - 19	Preservatives (antimicrobial agents)
Zwitterionic	 Cocoamidopropyl betaine	 Disodium laurethsulfosuccinate	Detergent, emulsifying agent, foam booster
Non ionic	 Cocamide DEA	 Polysorbate 20	Detergent, emulsifying agent, foam booster

4.2.1.1 Anionic Surfactants

Anionic surfactants possess a negatively charged head group. Industrial applications use this surfactant due to its low manufacturing costs and compatibility with a wide range of detergents. Linear alkyl chains ranging from 12-16 carbons provide an optimum detergency. They are preferred over branched chains since they are more effective and degradable. The most commonly used hydrophilic groups are carboxylates ($C_nH_{2n+1}COO^-X^+$) found in soaps, sulphates ($C_nH_{2n+1}OSO_3^-X^+$) used in detergents (with the most popular member of this group being sodium lauryl sulphate), sulphonates ($C_nH_{2n+1}SO_3^-X^+$) and phosphates ($C_nH_{2n+1}OPO(OH)O^-X^+$). The value of n ranges from 8-16 atoms and Na^+ the counter ion (Maibach H.I., 2001, Tardos T.F, 2005).

Soaps are sodium or potassium salts of fatty acids, produced by the reaction between fats or vegetable oils and alkali. This process is known as saponification (figure 4.6)

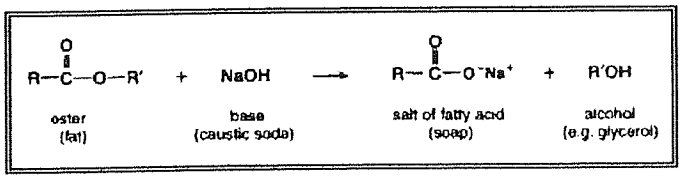


Figure 4.6 Saponifation process involving an ester and alkali to produce a salt a fatty acid and an alcohol

Soaps do not behave well in hard water because they react with calcium or magnesium ions forming a curd like precipitation. Soaps lack the cleaning power possessed by synthetic surfactants. Anionic surfactants are known to be harsh causing irritation of the eyes and scalp. They are not appropriate for use in personal care products in large quantities. However, sodium lauryl sulfate is one of the less irritating surfactants from this group. It has been incorporated in drugs for oral consumption, ranging from 0.004mg to 0.06mg, and in some topical creams lotions or ointments with the concentration ranging from 0.1% to 12.7%. Concentrations vary from less than 0.1% to more than 50% in personal care products which include hair shampoos, bubble baths, skin cleansing

products and moisturisers. Anti-irritant ingredients (e.g. aloe vera, allantoin) are incorporated into formulations to reduce the sensitivity. These types of surfactants are used in dishwashing detergents and washing powders. Many industrial and commercial applications use anionic surfactants in conjunction with non ionic surfactants, since they have greater stability.

Aerosol OT contains a sulfonate hydrophilic group and is synthesised by the esterification of sodium sulfosuccinate. This molecule has bulky hydrophobic groups relative to the hydrophilic group and is an excellent wetting agent. Incorporation in water based inks results in a reduction of surface tension, improving the adhesion, gloss and colour resolution. They can also be used to produce latexes (e.g. styrene- butadiene, vinyl acetate) by emulsion polymerisation and results in a low particle size (Barel A.O et al., 2001, Maibach H.I., 2001).

4.2.1.2 Cationic surfactants

Most cationic surfactants are based upon chemical compositions containing at least one or more nitrogen groups, as a source of positive charge and typical examples are given in table 4.1. Corresponding analogues contain either sulfur or phosphorous and are considerably more expensive than their nitrogen containing counterparts. Ammonium surfactants known as quats, retain their cationic character at any pH, as long as the molecule does not degrade. This class of surfactant has properties which include being able to foam, a non irritant to skin when used in small quantities and for numerous applications for example cosmetic, cleaning and antistatic preparations. The importance of cationic surfactants was realised over 50 years ago when their unique bacteriocidal properties were reported. Cetyl trimethyl ammonium bromide (CTAB) shown in table 4.1 is classified as an alkyl quat. It is one of the components of antiseptic cetrimide. It provides a buffering solution for the extraction of DNA (Maibach H.I., 2001, Tardos T.F, 2005, Farn R., 2006). Esterquats are used in fabric softeners prevent static cling, whilst providing softness to items of laundry. It is more environmentally friendly than its dialkyl counterpart. The positively charged nitrogen is attracted to the negatively charged fabric surface forming a weak ionic bond to the surface of the fabric.

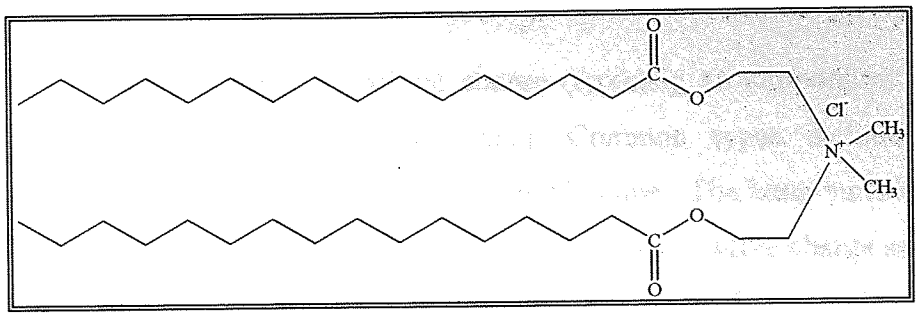


Figure 4.7 Esterquat

Cationic surfactants are incorporated into detergents, alongside anionic surfactants to improve the packing of these molecules at the stain/water interface. Robust dirt removal is achieved by these surfactants via an efficient method which results in the reduction of the stain/water interfacial tension. It is highly effective at removing greasy stains. Generally, this type of surfactant is included in shampoo or fabric softener formulations.

Quaternium-19 shown in figure 4.7 is incorporated in hair conditioner formulations to reduce or eliminate the build up of static electricity. Hair is composed of keratin, a protein which is predominantly made up of negatively charged amino acid building blocks. An increase in the conductivity of the hair results in the build up of a triboelectric charge, a direct result of positive charge removal from hair. Shampoos containing anionic surfactants are used to remove dirt from the hair. However, they also remove essential oils and the positive charges are required to maintain healthy hair. The positively charged surfactant is attracted to the negative charges and forms a thin film of detergent when it dries.

4.2.1.3 Zwitterionic surfactants

Zwitterionic surfactants possess a positive charge (typically an ammonium ion) and a negative charge (commonly carboxylate ions). Common types include N- alkyl derivatives of simple amino acids (e.g. glycine) and betaine. The latter surfactant carries a permanent positive charge whereas non betaines develop a positive charge as a result of protonation. Despite being highly compatible with other surfactants they are more expensive compared to the other classes. In an acidic or basic environment this type of surfactant remains stable, due to the presence of both positive and negative charges on the molecule.

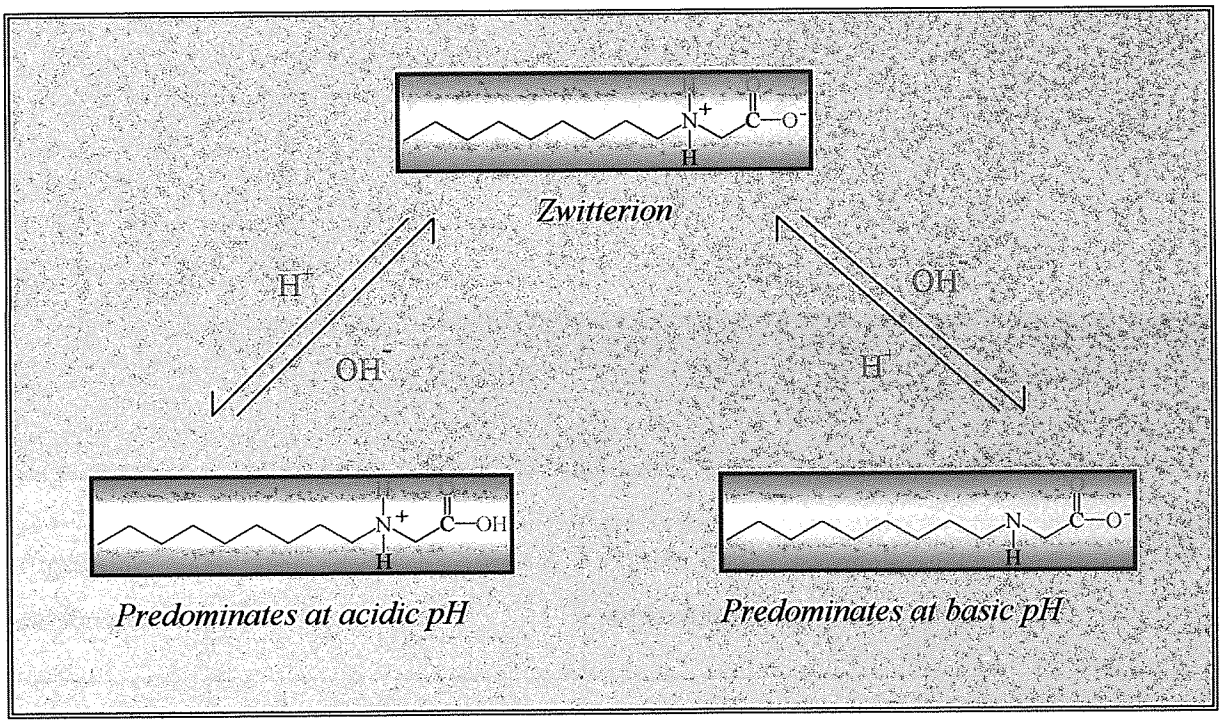


Figure 4.8 An illustration showing the change in chemical structure of a zwitterion when placed into either an acidic or basic environment

Placing a zwitterion into an acidic environment (figure 4.8) results in the addition of a proton onto the carboxylate ion ($-COO^-$) forming a carboxyl group (- COOH). This leaves a positive charge on the nitrogen atom. The addition of a base to a zwitterion results in

removal of a proton from the $-NH_2^+$ group. This changes it into –NH and a negative charge remains on the carboxylate group. Solubility of this type of surfactant is limited to the isoelectric point (equal charge) and can range from pH 2 to pH 9, depending upon the strength of the anionic and cationic groups. The mechanism which renders the surfactant water soluble is diminished causing a decrease in solubility. The addition of an anionic surfactant to a cationic one, results in the formation of a water insoluble complex, if the combined chain length is greater than twenty carbon atoms. However, the cationic group on the amphoteric surfactant can be used to promote greater packing. It reduces the repulsion between negatively charged groups under the conditions at which it dominates (Maibach H.I., 2001, Tardos T.F, 2005).

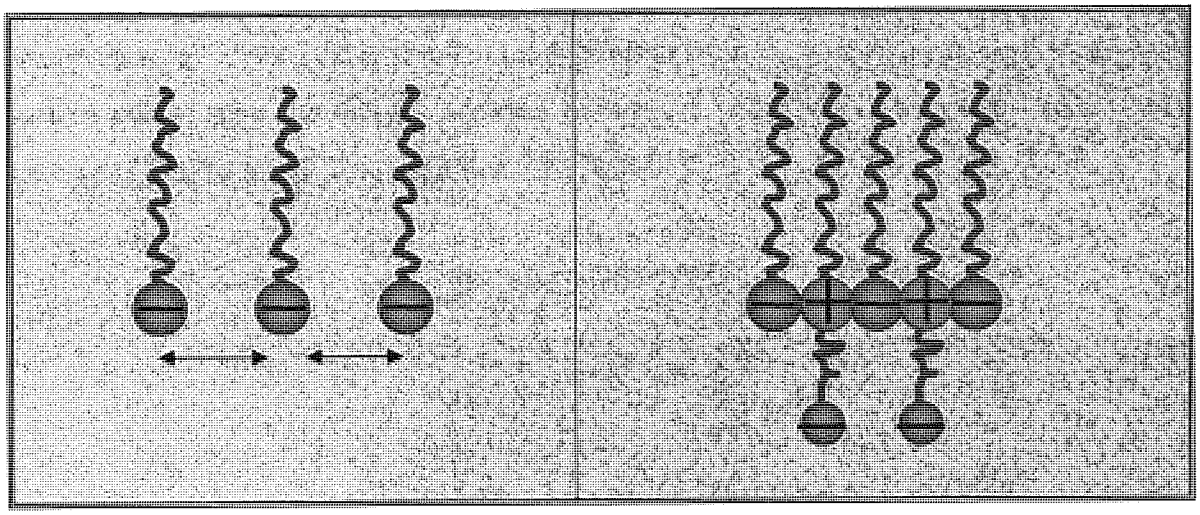


Figure 4.9 Packing between anionic surfactants	*Figure 4.10 Packing of anionic and cationic surfactants*

This class of surfactant possesses the detergent properties of anionic surfactants and the antibacterial properties of the cationic surfactants. Balanced zwitterionic surfactants are known to be non-irritating to the eyes and skin and are widely used in personal care products.

4.2.1.4 Non ionic surfactants

If required this type of surfactant can be used in conjunction with non charged surfactants. Generally, they are appreciated for their eye and skin compatibility. There are several classes of non ionic surfactants which are based upon the derivatives of ethoxylates e.g. alkyl ethoxylates, fatty acid ethoxylates, sorbitan ester ethoxylates and ethylene oxide- propylene oxide copolymers (referred to as polymeric surfactants).

Fatty acid esters of sorbitan known as Spans have corresponding ethoxylated products known as Tweens. They are commonly used in formulations manufactured for food and drug applications. Spans are produced by reacting sorbitol with a fatty acid at high temperatures (>200°C). This results in dehydration yielding 1, 4 sorbitan. Esterification is carried out to give the desired sorbitan monoester and figure 4.11 shows the general structure (Maibach H.I., 2001, Tardos T.F, 2005).

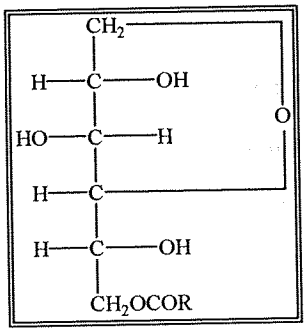


Figure 4.11 General structure of a sorbitan monoester

Ethoxylated derivatives of Span are produced by reacting ethylene oxide with a hydroxyl group which remains on the sorbitan ester group. An alternative route for production involves reacting with ethoxylate sorbitol followed by esterification. Generally, sorbitan esters are insoluble in water. They have a low HLB value and are good at forming a water in oil emulsion. The ethoxylated products have higher HLB values and are soluble in water. Ethylene oxide or propylene oxide polymers are classified as alkoxylated alcohols. PEG ethers known as the ethoxylated alcohols are produced by reacting fatty acids with ethylene oxide (EO). Using a similar method PPG ether (Polypropylene glycol ether) are

obtained with propylene oxide (PO). The HLB value of ethoxylated alcohols are adjusted by the balance of hydrophilic ethoxylated chain to the hydrophobic fatty chain. EO/PO surfactants are formed when a hydrophilic portion EO is combined with the hydrophobic portion PO. They are well known as poloxomers and Pluronics (trade mark of BASF) and have a block configuration. These surfactants exhibit low foaming properties and due to their mildness they are used in cosmetic applications. Generally, they are used as emulsifing, solubilising or fluidising agents.

4.3 Hydrophile- Lipohile Balance (HLB)

Griffin first defined the affinity of a non ionic surfactant in terms of an empirical quantity, the HLB. This is a number, calculated for each surfactant on an arbitrary scale of 1 to 20. Based upon the analytical or chemical composition data, the hydrophilic/ lipophilic balance of the surfactant is denoted. This value allows the relative affinity of the surfactant for an aqueous or organic phase to be determined. A low HLB value (3-6) represents lipophilic surfactants. They possess a low ratio of hydrophilic to lipophilic groups, which dissolve preferentially in oil, stabilise W/O emulsions and form reverse micelles in oil. A high HLB value (8-18) represents hydrophilic surfactants. They possess a high ratio of hydrophilic to lipophilic groups. They dissolve in water, stabilise O/W emulsions and form micelles in water. A surfactant with an intermediate HLB value (7-9) has no particular preference for oil or water and is considered to be a good wetting agent. Molecules with a HLB value above 18 are extremely hydrophilic and are often not particularly surface active. They tend to accumulate preferentially in bulk oil or bulk water rather than at the oil water interface. The uses of a surfactant can be derived from its HLB number as shown in table 4.3 (Binks B.P., 1998, Everett D.H., 1998).

HLB number range	Application
3-6	W/O emulsifier
7-9	Wetting agent
8-18	O/W emulsifier
13-15	Detergent
15-18	Solubiliser

Table 4.3 Application of surfactants based on their HLB number (Tardos & Vincent 1983)

4.4 Micellisation of surfactants

Geometric and energy factors limit the spontaneous growth of a micelle to a finite size. The concentration at which micellisation takes place is known as the critical micelle concentration (CMC). The contribution of the physical properties of the system are different to those of the individual molecule. The initial formation of micelles, typically contains a relatively small number of molecules (50 – 100) and are spherical in shape. At higher concentrations and under appropriate concentrations the spherical micelles may adopt a disc like, cylindrical, laminar or vesicle form (Everett D.H., 1998).

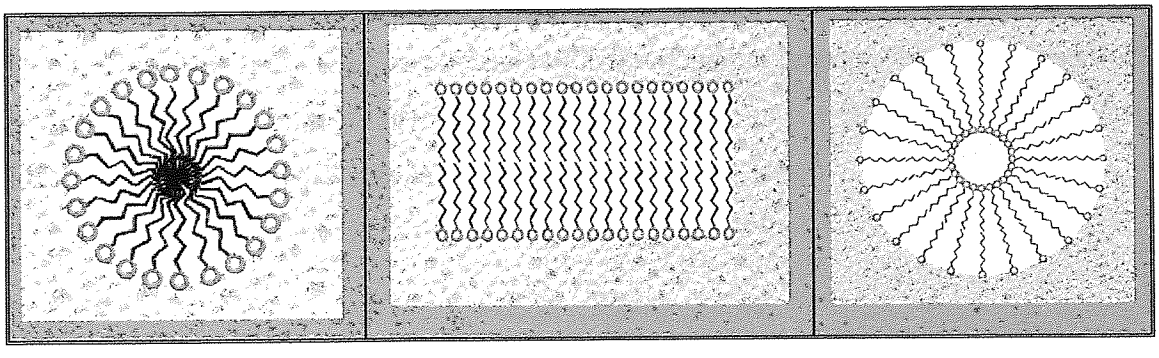


Figure 4.12 (From left to right) Disc like, lamellar and spherical vesicle micelles

The balance of an amphipathic molecule in solution is affected by the interactions of the hydrocarbon chains with water, the hydrocarbon chains with themselves, the solvation of the head group and the interaction between the solvated head group, in particular ionic groups. The HLB must be considered because an increase in the hydrocarbon chain results in a reduction of the CMC.

Geometrical, packing and energetic factors need to be considered. Micelles reduce the free energy of a system by minimising the area of contact between hydrocarbon chains and water. Maximum interactions are maintained between the hydrophilic moiety and water. The radius of the sphere must be the same length as the hydrocarbon chain. A longer hydrocarbon chain results in the embedding of the hydrophilic head groups in the hydrocarbon sphere. If the chain length was less than the radius, contact between the hydrocarbons and water would increase. Head groups cannot be closely packed on the surface of the sphere if hydrocarbons are to be accommodated in the core. Exposure of the hydrocarbon groups to the surface is required.

A balance between the repulsion of head groups leads to an increase in the area exposing hydrocarbon chains to water. Micelles are formed due to two competing factors. Firstly, micellisation is driven by transfer of hydrocarbon chains out of water into the oil like interior which is mainly due to entropy, known as the hydrophobic effect. The aggregations of surfactant in micelles are more ordered and have lower entropy than the free surfactant molecules dissolved in solution. The gain in entropy for the surrounding water molecules is small. Water molecules around a hydrocarbon chain are highly ordered. A drastic increase in entropy is seen when hydrophobic chains are hidden within the micelles. This more than compensates for the negative entropy for the aggregation of surfactant. The hydrophobic effect results in a decrease in the CMC with the increasing length of an alkyl chain (Binks B.P., 1998, Everett D.H., 1998).

A further consideration is that repulsion occurs when two polar head groups come together opposing aggregation. Head groups must be dehydrated before they approach each other resulting in hydration repulsion. In addition, the steric effects are a contributor. When the head groups come closer together their thermal fluctuations become smaller due to the confinement imposed by neighbouring head groups. Reduced mobility decreases the entropy and leads to repulsion. For charged head groups an additional electrostatic repulsion occurs due to additional energy requirements to bring these charges together. CMC's of ionic surfactants are much higher those for non ionic surfactants. The addition of a salt has a drastic effect on the micellisation of charged surfactants. An increase in the concentration of background salt causes the CMC of ionic surfactants to decrease. The salt effectively screens the electrostatic repulsion between the head groups. Energetically, it is easier to bring ionic surfactants together when the charges are screened.

4.5 Dermatological aspects of surfactants

A large number of dermatological problems occur when unprotected skin is exposed to large quantities of surfactant e.g. certain personal care and household cleaning items. Skin irritation is induced by the surfactant, whereas byproducts cause sensitisation, an allergic reaction. In 1960 the Netherlands was struck by the 'Margarine disease'. A new surfactant was added to ensure the fine dispersement of water particles during frying and the by product was an electrophile. It reacted with the nucleophilic groups on proteins, creating unnatural protein derivatives, detected by the body as foreign (Lees M., 2001).

Surfactants with larger head groups have a low binding affinity to proteins. Long chain length surfactants, have a higher surface activity due to their limited solubility and binding ability. At high temperatures, the solubility and binding ability of the longer chain length surfactants increase. Surfactants with a tendency to bind strongly to corneum proteins have a higher potential to cause denaturation. This can lead to barrier damage, erythema and itching. For certain applications, an anionic surfactant is required e.g. sodium lauryl ether sulfate. The addition of an amphoteric cosurfactant, cocoamido propyl betaine modified the activity of the surfactant due to the competition presented by

cosurfactant binding and co micellisation. The surfactant with a lower CMC value will preferentially be selected. The risk of irritation can be minimised by the introduction of a surfactant with a lower CMC value than the anionic surfactant. Co-micellisation is often synergistic resulting in lower CMC values than that of either surfactant added.

Water binding and holding capacity of proteins are significantly affected by surfactants. An increase in the net negative charge of the protein due to the surfactant binding causes an increase in the uptake of water, causing the skin to swell. The body regulates the water level at its natural rate after the skin has been washed, resulting in the loss of NMFs, responsible for maintaining the moisture levels.

The application of a surfactant, above its CMC, leads to delipidisation of the stratum corneum. The cholesterol, ceramides or fatty acids are solubilised within the micelle. Surfactants have the potential to increase the permeability of the lipid bilayers, resulting in their destabilisation. Anionic surfactants interact strongly with proteins and cause delipidisation. Low concentrations of non ionic surfactants cause delipidisation, whilst exhibiting minimal interactions with protein.

4.6 Aims

This chapter will illustrate the utilisation and development of monophasic gel technology, as highlighted in the previous section. Preliminary studies will be carried out to determine the polymerisability of hydrophobic monomers, containing an acrylate functional group. Free radical polymerisation was used to synthesise partially hydrated hydrophilic skin adhesives. Comparative studies are required on an identical initiating – crosslinking system.

Compatibility of a conventional NaAMPS pregel with a non ionic bridging monomer and a hydrophobic monomer has to be established. A range of hydrophobic monomers will be selected to investigate the effects of varying degrees of lipophilicity upon the structural integrity of a gel. The degree of hydrophobicity of the monomers differ, allowing a range of lipophilic and monophasic actives to be incorporated for the desired application.

The peel strength and mechanical properties of the biphasic skin adhesive hydrogels will be investigated to ensure that the incorporation of the hydrophobic monomer does not adversely affect the structural integrity or final application requirements.

4.7 Results

4.7.1 Thermal polymerisation of non adhesive biphasic hydrogels

Preliminary studies were carried out to investigate the polymerisability of epoxidised soybean oil acrylate (ESBA) with the following hydrophilic monomers, HEMA or N,N DMA. 0.1% w/w of AIBN a thermal initiator and 0.1% w/w of N,N methylene bis acrylamide a crosslinker were added in accordance to the method stated in section 2.3.1.1. Thermal polymerisation aided the copolymerisation of the bulky hydrophobic monomer with the hydrophilic monomer. Transparent, pale yellow, brittle gels were synthesised. The amount of ESBA contributed to the physical appearance of the gel. The intensity of colour increased proportionally with the amount of ESBA added.

ESBA (% w/w)	HEMA (% w/w)	N,N DMA (% w/w)
10	90	0
20	80	0
30	70	0
40	60	0
10	0	90
20	0	80
30	0	70
40	0	60

Table 4.4 Monomer compositions converted into polymers by thermal polymerisation

The reaction mechanism for the synthesis of the copolymers followed a typical free radical polymerisation. The decomposition of the initiator AIBN (Scheme 4.1) occurred at 50°C which generated two identical radical species. These highly reactive radicals can react with the vinyl groups on the monomers forming monomeric radicals. The addition of a difunctional crosslinker resulted in the formation of a radical at both ends of the chemical and links the monomeric radicals together. Scheme 4.1-4.3 shows the reaction

mechanism for the free radical copolymerisation of ESBA with HEMA. The propagation steps shown in scheme 4.2 highlight the simplest combinations of a free radical with a monomer. This is not a true representation of the number of possibilities. In essence, any radical species from the selection shown in scheme 4.1 has the potential to react with the monomer units and the crosslinker. The ESBA has three potential sites of attack by a free radical species, which occurs via addition from one of the following; initiator radical, HEMA or ESBA monomeric radical or an AIBN radical.

The crosslinker radical has the potential to react with the monomer radicals, if the electronic configuration of the other vinyl site has not been altered. Reactions with HEMA or ESBA monomer radicals are possible. Combinations of ESBA and HEMA radicals or vice versa have a high probability of occurring, due to their concentrations and compatibility when compared to the low concentration of crosslinker. A reduction in the number of monomer units and the crosslinker units produce a high concentration of free radicals. At this point a large number of radical chains exist and the reaction mechanism proceeds to its final step, known as termination. This involves the consumption of free radicals resulting in non adhesive gels.

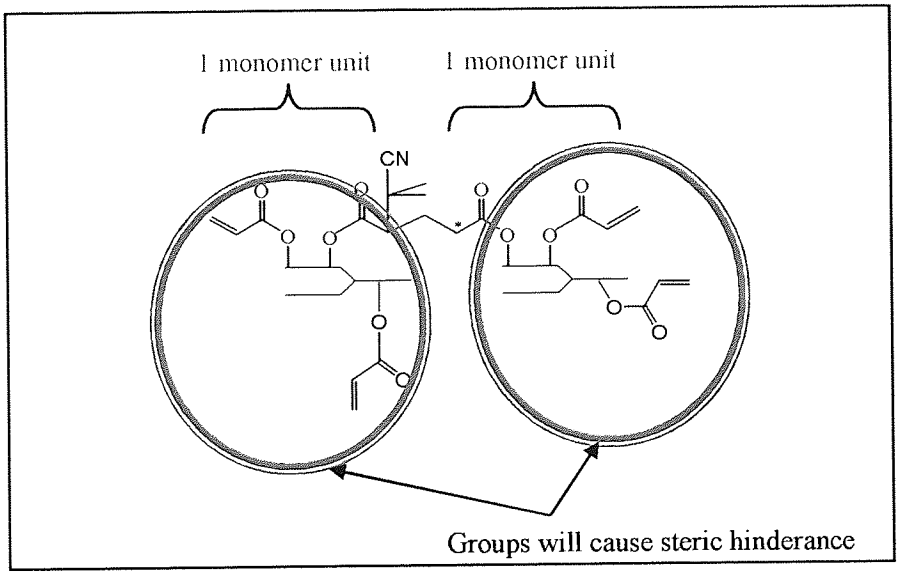


Figure 4.13 Steric effects caused by the bulky groups on the ESBA monomeric radical

There are two principal methods of termination in free radical polymerisation; combination of two free radicals and the other disproportionation, involving the transfer

of a hydrogen atom from one chain end to the other. The structure dictates the method of termination, specifically the chain end radical. In general, both processes of termination will occur. Disproportionation will be favoured for an ESBA radical structure if there are two units adjacent to each other (scheme 4.3), if it possesses two large bulky groups on either side of the radical. Combination occurs with HEMA if the vinyl group is available as shown in scheme 4.3. An initiator molecule adjacent to an ESBA monomeric radical, results in steric hinderance. This would considerably lower the reactivity with another free radical e.g. MBA the crosslinker, therefore it would undergo combination. The presence of an ester group results in electrostatic repulsion, which would increase the activation energy for the coupling process.

A HEMA end radical has more α hydrogens (figure 4.14) than the ESBA end radical which possesses two. Therefore, the HEMA radical at the end of the chain will donate a hydrogen radical resulting in disproportionation. The replacement of HEMA by the N,N DMA alters the termination process. The N,N DMA end radical as shown in figure 4.14, possesses two α hydrogens and lacks the methyl groups, known to cause steric hinderance, thereby terminating via combination. Reaction with a radical species which does not result in electrostatic repulsion is preferable.

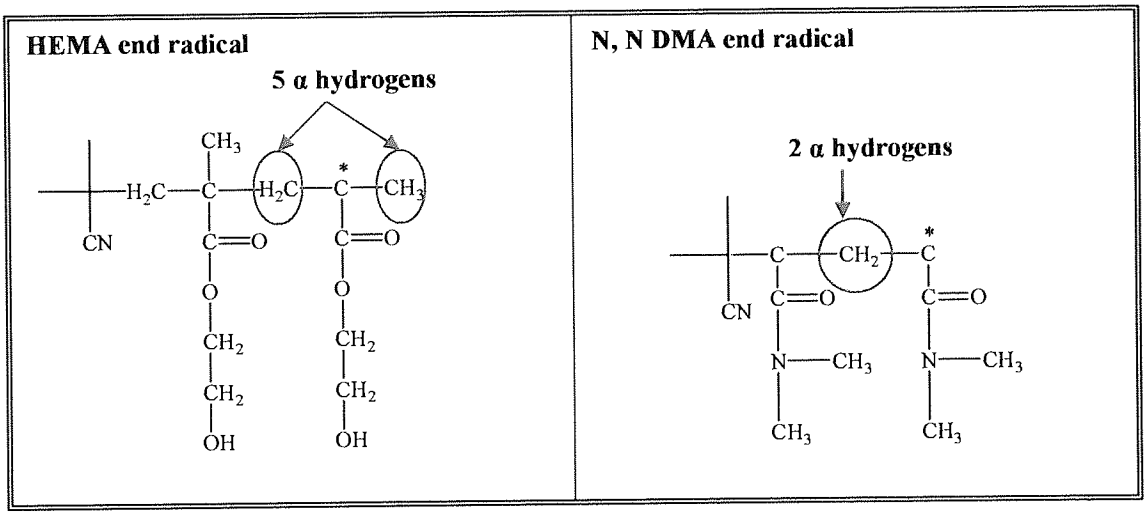
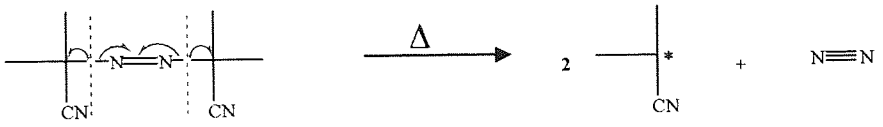
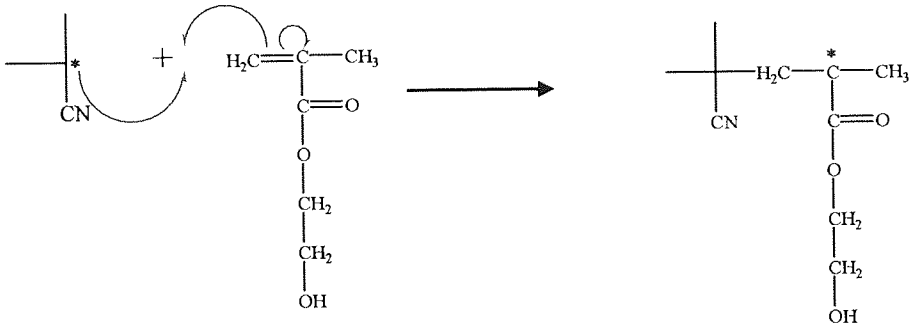


Figure 4.14 Alpha hydrogens on a HEMA end radical unit and a N,N DMA end radical

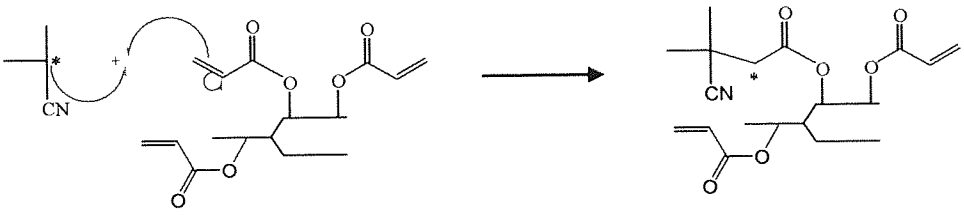
Initiation



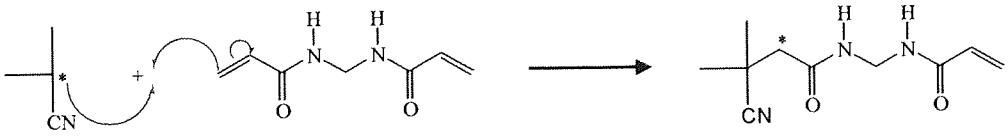
Thermal decomposition of AIBN at 50°C generates two initial free radicals and N_2 as a by product.



The chemical reaction involves a primary free radical and the vinyl group on HEMA. This forms the corresponding free radical monomer unit.



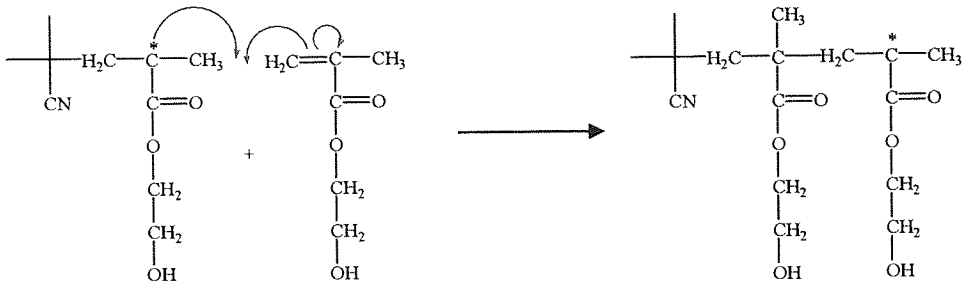
The reaction involves a primary free radical and one of the vinyl groups on the ESBA monomer, which forms the corresponding free radical monomer unit.



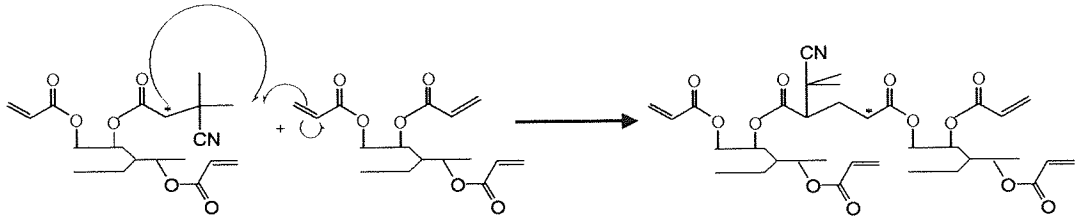
A chemical reaction involving an initial free radical and one of the vinyl groups on the crosslinker, forming a free radical with at the vinyl sites

Scheme 4.1 Free radical thermal initiation reaction mechanism

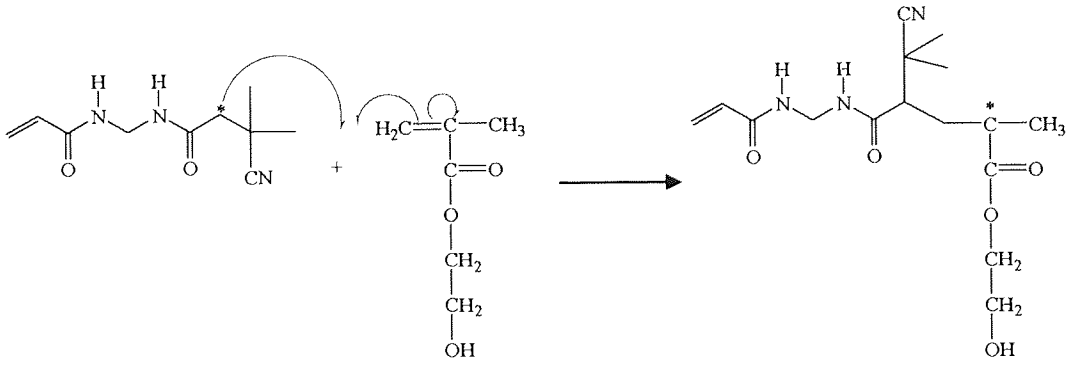
Propagation



Addition of a HEMA monomer free radical (RM^*_{HEMA}) unit to a HEMA monomer unit (M_{HEMA}) resulting in the chain growth process.



Addition of an ESBA free radical (RM^*_{ESBA}) unit to an ESBA monomer unit (M_{ESBA}) enabling polymer chain growth.

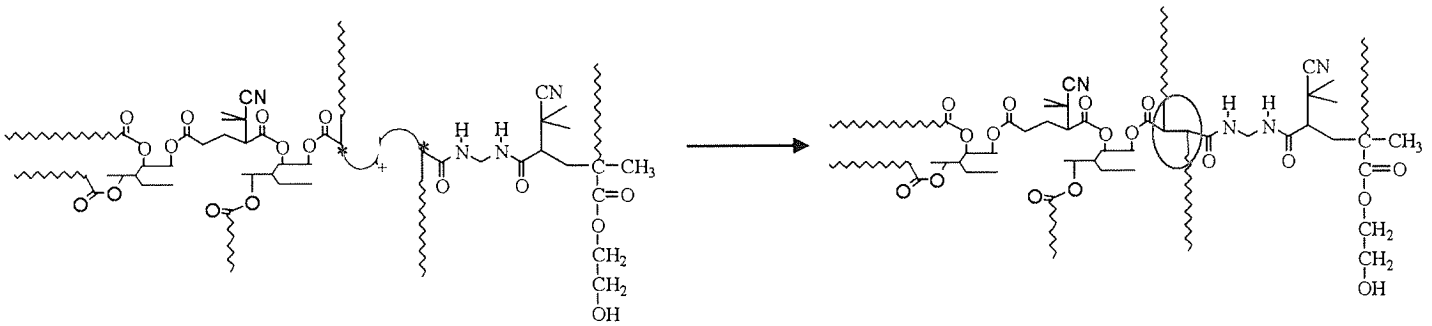


Addition of an MBA free radical (RMBA*) unit to a HEMA monomer unit (M_{ESBA}) which acts a crosslinker. It aids the polymeric chain growth whilst contributing to the 3D matrix.

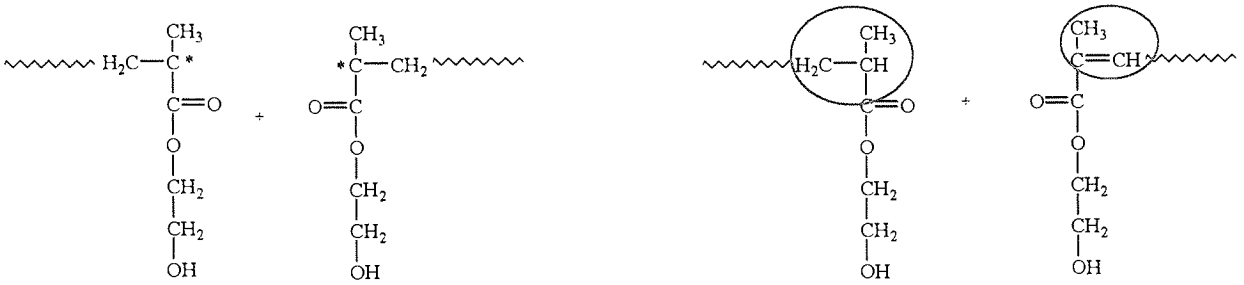
A vast number of other combinations are possible and they are not limited to the ones shown as explained previously.

Scheme 4.2 Free radical propagation reaction mechanism

Termination



Termination process occurring when an EBSA radical comes in the vicinity of an MBA radical forming the 3D polymer matrix via combination.



The disproportionation process occurs when two HEMA radicals are in the vicinity of each other resulting in the loss of a hydrogen radical from one species to the other as shown.

The two main methods of termination are highlighted above and combinations of both types occur during this stage of free radical polymerisation.

Scheme 4.3 Free radical termination reaction mechanism

4.7.2 UV polymerised non adhesive biphasic hydrogels

The non adhesive biphasic hydrogels shown in table 4.4 were synthesised using an alternative free radical generating chemical, 0.1% w/w of Irgacure 184. This UV initiator was incorporated into the formulation. It required wavelengths ranging between 240-250 and 325-333nm to induce dissociation. Initially, these set of experiments were carried out to ensure that epoxidised soybean oil acrylate could be photopolymerised with a widely used industrial technique. The gels produced were pale yellow and brittle, similar to those produced thermally.

A comparative study of the two techniques used for polymerisation highlighted that UV polymerisation is a quick, effective method and takes less than ten seconds, compared to thermal polymerisation which requires at least three days. Therefore, further synthesis work focuses on this technique.

4.7.3 Equilibrium water content of the non adhesive biphasic hydrogels

The gels produced in section 4.7.1 and 4.7.2 were immersed in distilled water for five days for hydration. The EWC values were measured as stated in section 2.3.2.5. The gels produced by thermal polymerisation highlighted that an increase in the percentage of hydrophobic monomer resulted in the decrease of the EWC value. A decrease in the percentage of hydrophilic monomer resulted in the reduction of sites that could interact with the water through hydrogen bonding. A gel consisting of 10% w/w of ESBA and 90% w/w of N, N DMA gave an EWC of 64.10%, a high value for a two phased hydrogel.

The incorporation of N,N DMA resulted in gels with approximately twice the EWC values than their HEMA counterparts. Therefore, it can be concluded that both HEMA and N,N DMA are compatible with ESBA. The incorporation of N,N DMA is compatible within both hydrophobic and hydrophilic solutions.

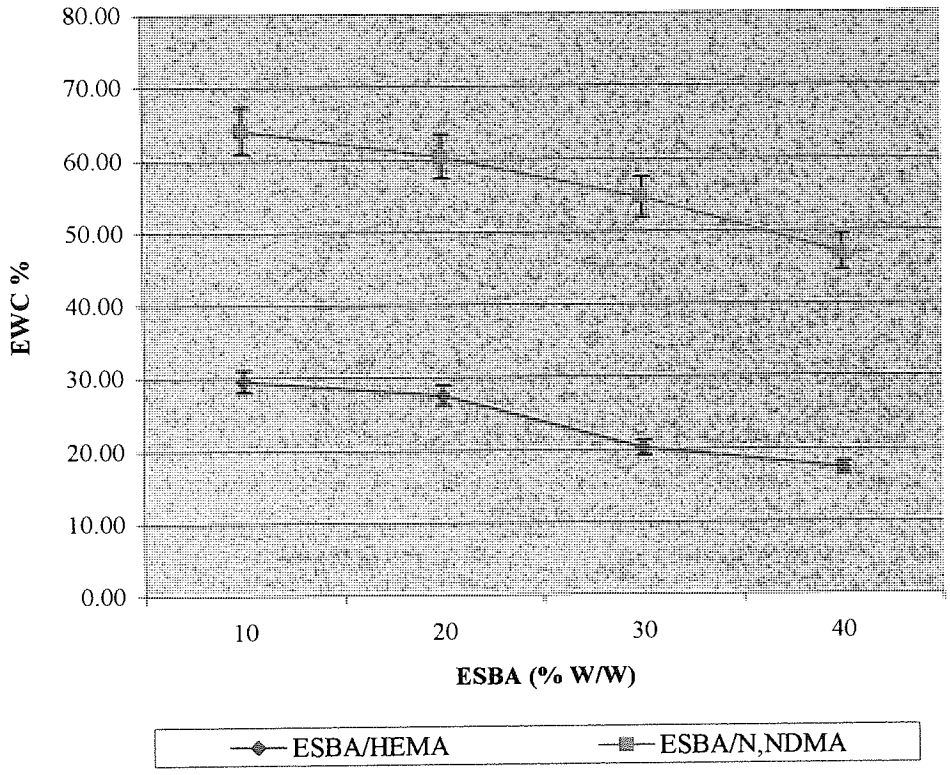


Figure 4.15 Equilibrium water contents of biphasic hydrogels synthesised by thermal polymerisation

The main technique used for hydrogel synthesis within this thesis was UV polymerisation. A comparative study was carried out on the same formulations with the thermal initiator replaced by a UV initiator. Figure 4.15 shows a similar trend for both thermally and UV polymerised gels, N,N DMA is more hydrophilic than HEMA. The EWC was not compromised using the UV polymerisation technique, instead slightly higher values were achieved. This can be accounted for by the change in initiator, showing that Irgacure 184 is more hydrophilic than AIBN the thermal initiator.

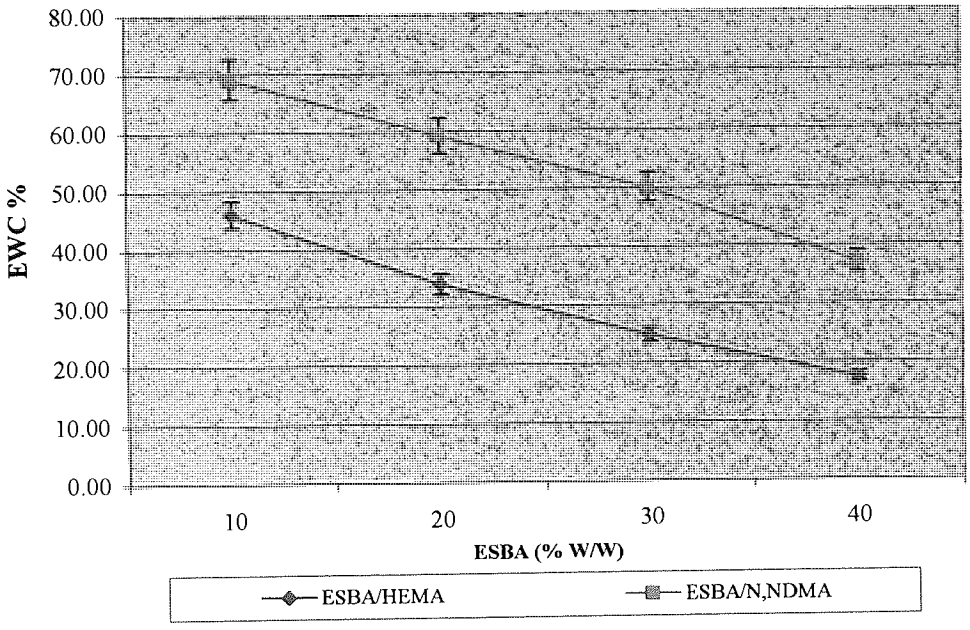


Figure 4.16 Equilibrium water contents of biphasic hydrogels synthesised by UV polymerisation

4.9.4 Selection of an appropriate bridging monomer

4.7.4.1 Incorporation of N,N DMA as a bridging monomer in a biphasic gel

A basic composition used in the synthesis of monophasic hydrogels (40% w/w of monomer, 25% w/w of glycerol and 35% w/w of H_20) was modified to allow the incorporation of the bridging monomer N,N DMA and the hydrophobic monomer ESBA. The amount of water, glycerol and bridging monomer were kept static throughout these experiments in order to optimise the amount of hydrophobic and hydrophilic monomers. Table 4.5 shows the monomer compositions and also the observations of the gel condition. 0.3 % w/w of Irgacure 184 the photoinitiator and Ebacryl II the crosslinker was added from a stock solution 3:10 ratio respectively.

NaAMPS (% w/w)	ESBA (% w/w)	*N,N* DMA (% w/w)	Description of the hydrogel
30	0	10	Transparent cohesive gel
27	3	10	Transparent cohesive gel
24	6	10	Transparent cohesive gel, slight tackiness on the surface
21	9	10	Tacky transparent gel
18	12	10	Very tacky transparent gel
15	15	10	No gel formation
12	18	10	No gel formation

Table 4.5 Compositions and polymerisabilty of biphasic hydrogels

Biphasic hydrogels containing a lower percentage of ESBA yielded gels with good cohesive properties, a prerequisite of skin adhesive hydrogels. The ideal composition for the biphasic gels was composed of NaAMPS, ESBA and N,N DMA at a ratio of 27:3:10 respectively. The levels of residual monomers were low when compared to the other compositions in table 4.5. The experiments highlighted, that if the percentage of ESBA exceeded the amount of bridging monomer, it resulted in phase separation and no gel was formed. From a formulatory perspective the bridging monomer was incorporated to ensure the distribution of the hydrophobic monomer throughout the hydrophilic components. The interactions between the hydrophobic (figure 4.17) and the hydrophilic monomer (figure 4.18) with the bridging solvent are shown. The methyl or the vinyl groups could be in contact with the ESBA and therefore presents a cage effect around the hydrophobic component. This protects it from the aqueous environment until the point of

polymerisation. The movement of the solvent bridge during the stages of initiation and propagation depend upon the location of a NaAMPS monomer radical. N,N DMA has the ability to interact with hydrophilic components, within the formulation, via hydrogen bonding at two sites (figure 4.18). This results in the cohesive nature of the gel. If there is an excessive amount of the solvent bridge within the formulation it can fulfill its multiple roles.

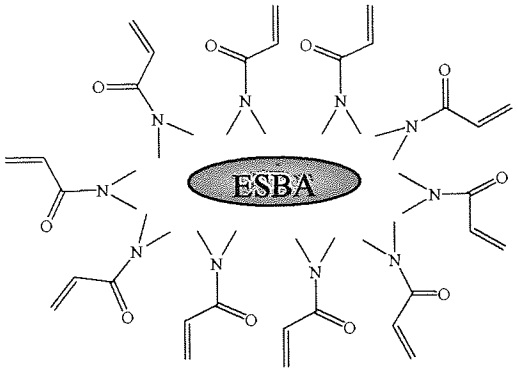


Figure 4.17 Interaction of N,N DMA a solvent bridging monomer with ESBA

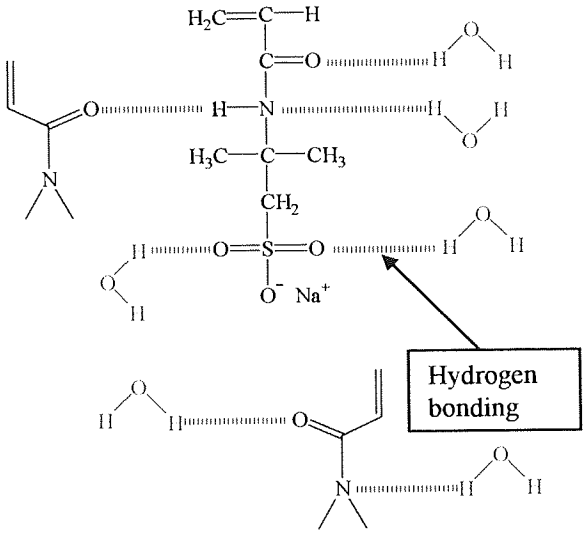


Figure 4.18 Interaction of N,N DMA with NaAMPS and H_20

4.7.4.2 Alternative bridging monomers

The incorporation of a suitable bridging monomer was essential to the distribution of the hydrophobic monomer in a pregel formulation. This ensured that phase separation did not occur before polymerisation. Investigative studies of two hydrophilic monomers, NVP and AMO highlighted that they possessed the essential characteristics which allowed them to interact with both hydrophilic and hydrophobic media.

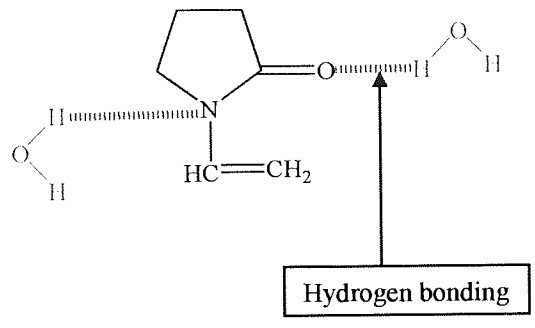


Figure 4.19 Hydrogen bonding between NVP and H_20

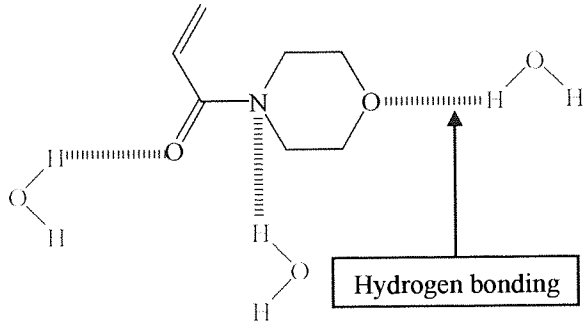


Figure 4.20 Hydrogen bonding between AMO and H_20

The compositions selected from 4.7.4.1 contained 6 % w/w of ESBA (using identical amounts of PI/XL mixture) to enable a comparison to be made between the different monomer bridges. Figure 4.19 and 4.20 show that NVP has two available sites to hydrogen bond and AMO has three sites. These sites are not limited to interact with water, they can also interact with the hydrophilic monomer. Gels containing NVP as the bridging monomer gave off a potent smell suggesting that residual NVP was present. This also indicated its lack of polymerisability within these formulations. The compositions containing AMO allowed 6 % w/w of ESBA to added and resulted in tacky gels with good cohesive strength. Taking into consideration that the gels are based upon hydrophilic compositions, the gels containing AMO did not give of an odour. It was compatible with both hydrophilic and hydrophobic components compared to those used previously. This solvent bridge was selected for use in further formulations.

NaAMPS (% w/w)	ESBA (% w/w)	NVP (% w/w)	AMO (% w/w)	Description of the hydrogel
24	6	10	0	Opaque white gel, poor adhesivity
18	12	10	0	Opaque white gel, poor adhesivity
9	21	10	0	Opaque white gel, poor adhesivity
24	6	0	10	Tacky transparent gel, good cohesivity
18	12	0	10	No gel formation
9	21	0	10	No gel formation

Table 4.6 Compositions of biphasic hydrogels containing either NVP or AMO as a bridging monomer

4.7.5 Modification of skin adhesive formulation to incorporate a suitable surfactant

4.7.5.1 Incorporation of a non ionic block surfactant

The presence of a solvent bridging monomer in a biphasic hydrogel composition allowed the incorporation of a low percentage of hydrophobic monomer, as determined in previous sections. The incorporation of this monomer enabled the distribution of ESBA throughout the pregel, however its mobility was restricted. Figure 4.17 shows the way in which ESBA is temporarily encapsulated, resulting in a hydrophobic central area. The solvent molecules have the ability to move and this can result in the destabilisation of the ESBA throughout the hydrophilic domain. This will ultimately result in phase separation of the pregel. The amount of bridging monomer was increased to approximately six times the amount of the hydrophobic monomer. The gels synthesised showed that it was

essential to incorporate a surfactant. Due to the hydrophobicity of the monomer a surfactant Pluronic P65 (HLB 12-18), F108 (HLB 24), or non ionic block copolymers of ethylene oxide/ propylene oxide were added to the formulation to promote the distribution of the hydrophobic monomer in the pregel.

NaAMPS (% w/w)	ESBA (% w/w)	AMO (% w/w)	NVP (% w/w)	*N,N* DMA (% w/w)	P65 (% w/w)	P108 (% w/w)
28	5	18.5	0	0	0.5	0
28	5	0	18.5	0	0.5	0
28	5	0	0	18.5	0.5	0
28	5	18.5	0	0	0	0.5
28	5	0	18.5	0	0	0.5
28	5	0	0	18.5	0	0.5

Table 4.7 Compositions of biphasic hydrogels containing a different bridging monomer in combination with a non ionic surfactant

Gels containing P65 were opaque and white. They showed visible signs of ESBA on the gel surface. This demonstrated that the surfactant was not compatible with the hydrophobic material. The surfactant was changed and P108 was used as a replacement. This resulted in tacky, pale yellow, opaque gels with no visible signs of aggregation of the ESBA on the top surface of the gel. However, ESBA was visible throughout the gel matrix highlighting its uneven distribution. Ideally, the polypropylene oxide should interact with the hydrophobic monomer whilst the polyethylene oxide interacts with the aqueous phase. The size of this surfactant was very large and had the potential to encapsulate large amounts of hydrophobic monomer. Despite the various compositions

containing P108 surfactant, the desired distribution of the hydrophobic monomer did not have a dramatic effect on the peel strength of the gels. The gels were peel tested using the method stated in 2.3.2.2 on a stainless steel substrate. The UV cured compositions gave similar results and were higher than the First Water standard NaAMPS gel (FW206TA7M) which gave a peel strength of 10.05 N/25mm. The gels were subjected to a post cure process of gamma radiation. Peel tests yielded higher peel strengths for the AMO and NVP compositions which are accounted due to the reduction of residual monomers. The post curing of the N,N DMA composition resulted in a reduction in the peel strength, which can be attributed to the reduction of residual monomers which led to a different polymeric conformation to the latter, promoting lower adhesivity. Smaller hydrophobic domains distributed evenly throughout the polymer matrix are required.This led to the study of alternative non ionic surfactants.

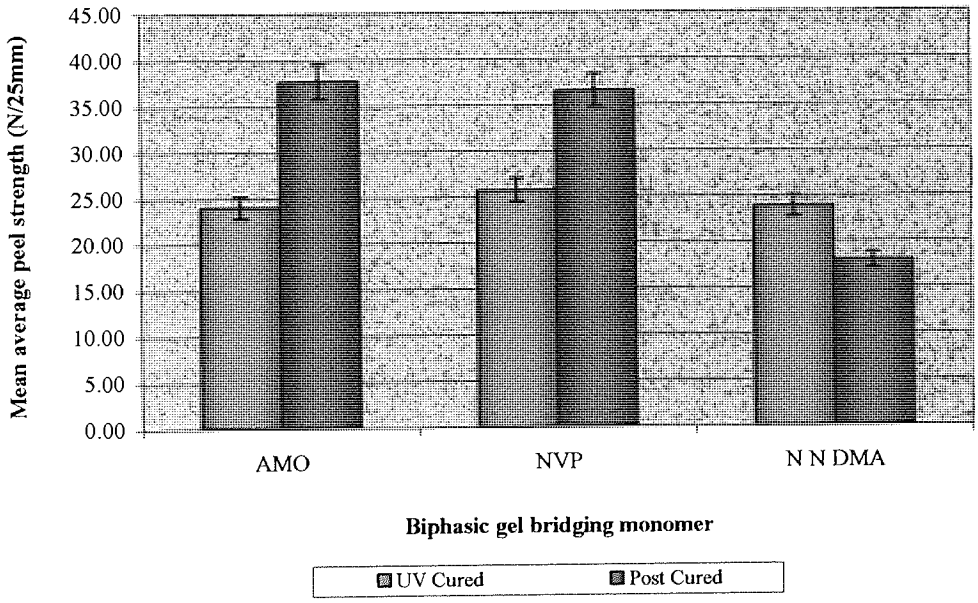


Figure 4.21 NaAMPS-ESBA biphasic hydrogels containing a different bridging monomer and a surfactant P108

4.7.5.2 Incorporation of a suitable non ionic surfactant

The addition of a non ionic surfactant to a biphasic gel resulted in the production of adhesive gels which showed no visible signs of phase separation, compared to those gels composed in previous sections. This class of surfactant was selected, since it is less irritating to the skin when compared to the other types available. Also the non ionics would not interact physically with other chemicals within the pregel, deterring them from carrying out their role within the three dimensional polymer matrix.

NaAMPS (% w/w)	**AMO (% w/w)**	**ESBA (% w/w)**	**PEG Myristyl tallow ether (% w/w)**	**Tween 20 (% w/w)**	**Tween 60 (% w/w)**
28.0	19.0	5.0	0.6	0	0
28.0	19.0	5.0	0	0.6	0
28.0	19.0	5.0	0	0	0.6

Table 4.8 NaAMPS-ESBA biphasic hydrogels containing AMO as the bridging monomer with surfactants with different HLB values

This section highlights that the HLB value gives a guide to the type of emulsion that is formed. Non ionics were selected within the HLB range of 8 to 18. Surfactants in this range are known to aid in the production of O/W emulsions. All of the gels formed showed no visible signs of phase separation. Therefore the hydrophobic material was encapsulated within the surfactant micelles. However, the peel tests showed that despite successfully synthesising the biphasic gels, there were other parameters that must be taken into consideration. Figure 4.22 highlighted that the gel containing PEG myristyl

tallow ether (PEG mte) had the lowest peel strength whereas the gel containing Tween 60 resulted in a peel strength approximately twice the former.

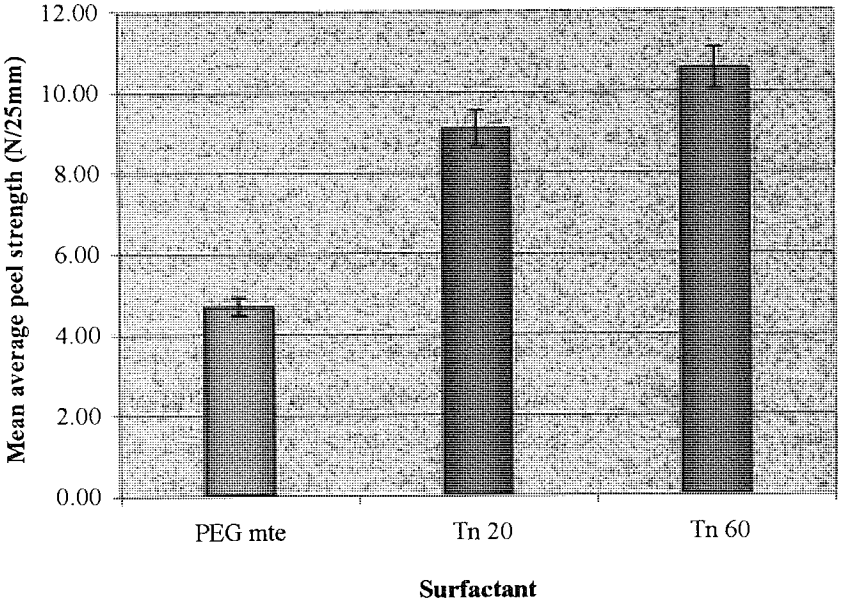


Figure 4.22 Biphasic hydrogel compositions containing the surfactant PEG mte, Tween 20 or Tween 60

The table below highlights the approximate molecular weights and the HLB values of the surfactants used in this section. The PEG mte has a higher ratio of hydrophilic to lipophilic groups which preferentially dissolve in water when compared to Tween 20 and Tween 60. The surfactants have different molecular weights but the HLB is of importance. A reduction in the HLB value from 17 to 16.7 results in the peel strength approximately doubling and the difference in structure is accountable. Ideally, the surfactant must interact with both the hydrophobic material and the hydrophilic components of the pregel in order to achieve a homogeneous solution. PEG mte has the tendency to interact with the hydrophilic chemicals more so than the hydrophobic chemicals. The polyethylene glycol part attracts water, glycerol and the hydrophilic monomers resulting in hydrogen bonding. This forms a good cohesive gel. However, the components are tied up with these interactions which lower the adhesivity potential. Complete solubilisation of the hydrophobic monomer thereby restricts the interaction

with the substrate used in the peel tests causing a decrease in value. The incorporation of Tween 20 or Tween 60 into hydrogel compositions gave similar results with the latter having a higher peel strength. When compared to PEG mte these surfactants are more mobile, which allow migration of the micelle during the polymerisation process. This ensures that the gel can be loaded with hydrophobic actives and can be released topically. The lower HLB value results from the encapsulation of the hydrophobic monomer with an optimum interaction with the hydrophilic domain. This is more predominant in gels containing high HLB valued surfactants. They possess a higher ratio of hydrophilic groups, which preferentially interact with the hydrophilic matrix.

Surfactant	Molecular weight	HLB Value
PEG mte	~3000	17.0
Tween 20	~1228	16.7
Tween 60	~1311	14.9

Table 4.9 Molecular weights and HLB values of PEG mte, Tween 20 and Tween 60

Incorporation of a surfactant with a different HLB value allows the adhesive strength to be altered. This allows the gels to be tailor-made for the peel strength required without having to change the ratio of all the components within the biphasic hydrogel.

4.7.5.3 Optimum amount of surfactant

As determined in the previous section, the incorporation of Tween 60 in biphasic gels results in an adhesive strength that is similar to that of a NaAMPS gel. An increase in the ratio of hydrophobic to hydrophilic groups causes a reduction of the adhesive bond due to the heterogenous environment. This section investigates the optimium amount of surfactant required within the pregel mixture ensuring that a homogeneous pregel is formed. Table 4.10 show that the compositions consisted of NaAMPS as the unsaturated hydrophilic monomer, AMO a bridging monomer, ESBA a bulky unsaturated hydrophobic monomer and Tween 60.

NaAMPS (% w/w)	**AMO (% w/w)**	**ESBA (% w/w)**	**Tween 60 (% w/w)**
28.0	19.0	5.0	0.6
28.0	19.0	5.0	0.9
28.0	19.0	5.0	1.2

Table 4.10 NaAMPS-AMO-ESBA biphasic hydrogel compositions containing varying quantities of Tween 60

The peel strengths illustrated that all of the gels had an acceptable level of adhesion and the gel containing 0.9 % w/w yielded the higher adhesive strength. Overall, low quantities of surfactant were used to limit skin irritations. They occur if an excessive amount of surfactant was added. With a restriction placed upon the amount of surfactant that can be added this in turn governs the amount of hydrophobic monomer that can be added. It is important to understand the interaction between the surfactant and hydrophobic monomer within the predominantly hydrophilic environment. Figure 4.24 shows that when 0.6 % w/w of Tween 60 was added, all the hydrophobic monomer was

not solubilised by the surfactant. Free hydrophobic monomer disrupted the adhesive bond which resulted in a lower peel strength.

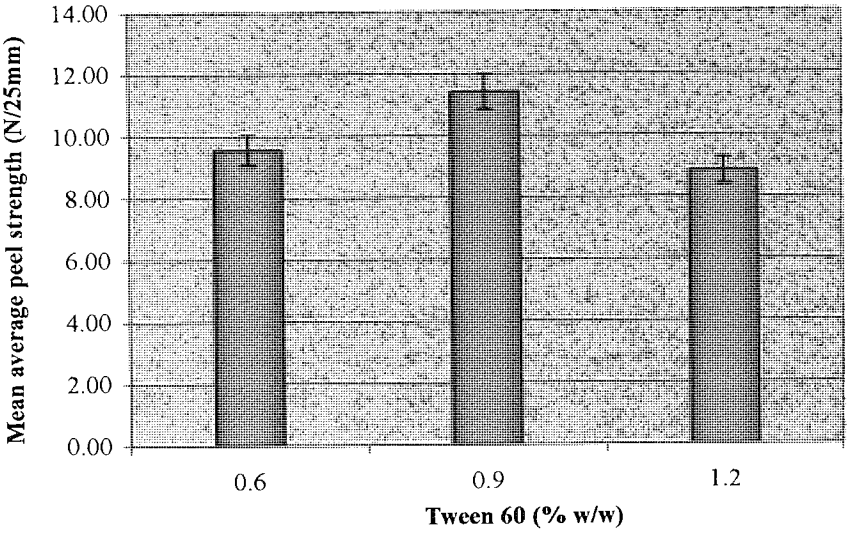


Figure 4.23 Peel strengths of poly(NaAMPS-AMO-ESBA) biphasic hydrogel compositions containing varying quantities of Tween 60

The addition of 0.9 % w/w of Tween 60 gave rise to the ideal situation. All of the hydrophobic monomer was solubilised. It was situated within a micelle structure yielding the highest peel strength. Finally the presence of 1.2 % w/w of Tween 60 in the composition resulted in the peel strength decreasing slightly. The excess amount of surfactant lowered the peel strength as highlighted in a previous chapter.

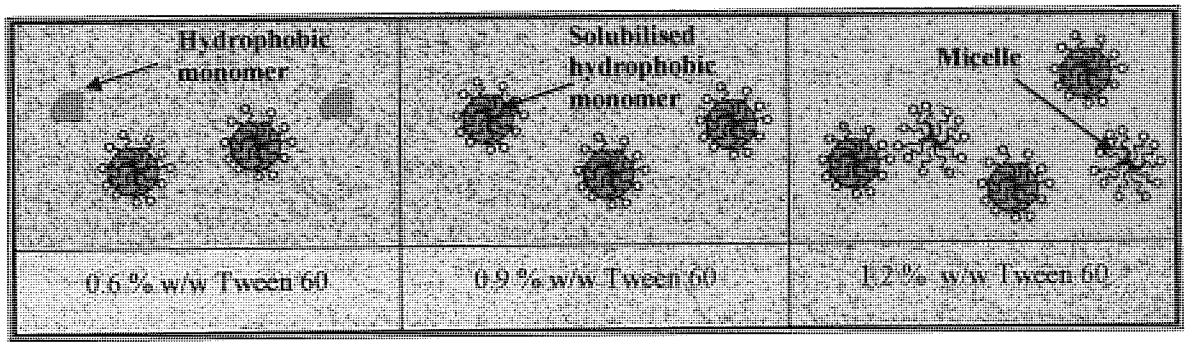


Figure 4.24 Diagram showing the varying degrees of solubilisation with a change in surfactant concentration

4.7.6 Selection of a suitable hydrophobic monomer

4.7.6.1 Incorporation of an alternative to ESBA

ESBA is a large bulky hydrophobic monomer and therefore butyl acrylate was selected as an alterative. This monomer was chosen due to its smaller size. Therefore its movement throughout the gel was anticipated to be quicker than that of ESBA. The compositions listed in table 4.11 were used to investigate the quality of gels formed when a range of bridging monomers were incorporated in the formulation.

NaAMPS (% w/w)	Butyl acrylate (% w/w)	AMO (% w/w)	NVP (% w/w)	*N,N* DMA (% w/w)
28.0	5.0	18.5	0.0	0.0
28.0	5.0	0.0	18.5	0.0
28.0	5.0	0.0	0.0	18.5

Table 4.11 Biphasic hydrogel compositions containing butyl acrylate as the hydrophobic monomer with various bridging monomers

The peel strengths achieved with this hydrophobic monomer in combination with the bridging monomers were substantially greater than those obtained from the biphasic gels containing ESBA. Taking into consideration F108, a pluronic based surfactant was incorporated into this formulation it highlighted that it is possible to use that type of copolymeric surfactant in conjunction with a smaller more mobile and less lipophilic monomer. These gels were post cured with gamma rays to ensure that any residuals had reacted. The cohesive and adhesive strength of these gels were excellent, unfortunately the incorporation of butyl acrylate from a synthetic perspective resulted in no further investigations into this hydrophobic monomer.

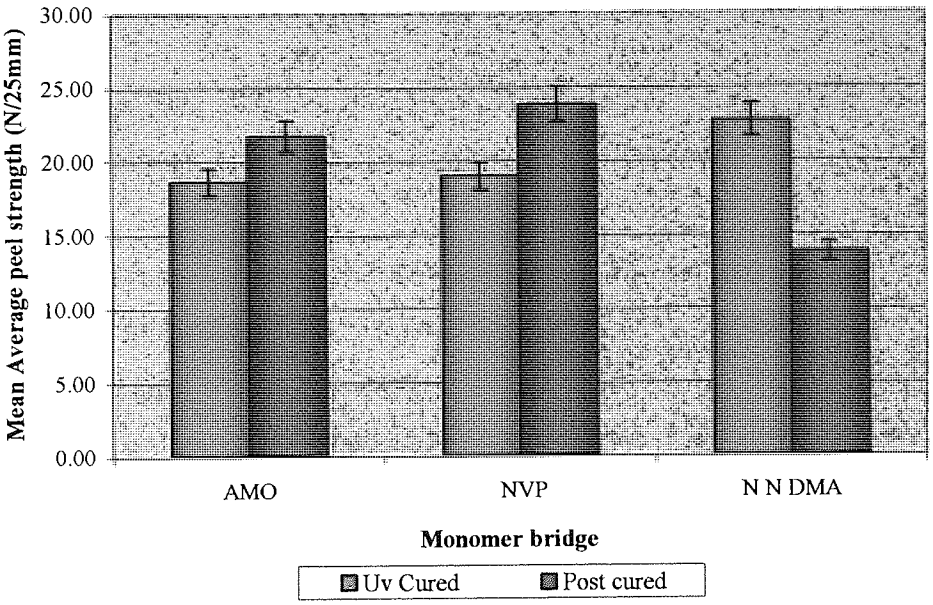


Figure 4.25 Butyl acrylate containing biphasic hydrogel compositions containing different bridging monomers

The monomer before polymerisation gave off a very potent smell which made it difficult to work with. Taking into consideration that this could potentially be used industrially, the dominating odour hindered its use with UV polymerisation. After the post cure process the butyl acrylate had polymerised fully and no residuals were present. An ideal hydrophobic monomer should not give off an odour during pregel preparation and also must be less bulky than ESBA, allowing it to be more mobile. This would ensure that the adhesive and cohesive strength of the gel were not compromised.

4.7.6.2 Incorporation of suitable hydrophobic monomers

4.7.6.2.1 Compatibility of Lauryl acrylate (LA) & Stearyl acrylate (SA) in biphasic skin adhesive compositions

Previous investigations have shown that ESBA a hydrophobic monomer was compatible with the bridging monomer AMO. Taking into consideration the size of the hydrophobic monomer was substantial when compared to the smaller hydrophilic monomers, which are predominant in the various hydrogel compositions. This essentially increases the probability of phase separation occurring. Compositions containing butyl acrylate were not acceptable despite yielding high peel strengths and its compatibility. Due to the potent smell of the monomer it was difficult to work with in the laboratory. However of greater importance if used industrially with UV polymerisation techniques, this would be unacceptable. Alternative hydrophobic monomers LA and SA were selected.

Lauryl and stearyl acrylate have molecular weights 240.38 and 324.54 respectively which are smaller and will potentially be more mobile than ESBA. The addition of AMO to LA or SA resulted in the formation of a semi opaque white solution. However, the incorporation of Tween 60 with either LA or SA resulted in a homogeneous solution when heating to 50°C, whilst mixing at 200 revs/min. The addition of AMO resulted in a clear transparent solution showing that it was homogenous. The order in which the chemicals were added was of great importance, otherwise it resulted in phase separation. The first step must involve the encapsulation of the hydrophobic material within a micelle structure. This ensures that contact between the hydrophobic and hydrophilic components are kept to a minimum. This reduces the interfacial tension that would exist between a hydrophobic chemical in contact with a hydrophilic structure. When the AMO was added it allowed the micelles to be distributed evenly and resulted in an oil in water emulsion. At this stage the speed of mixing was lowered to 50 revs/min to ensure that the emulsion was not destabilised. In a separate mixing vessel all of the hydrophilic components were mixed together and heated to 50°C.

The hydrophilic solution was added slowly, to ensure that enough time was given for the solvent bridging monomer to stay in close proximity to the micelles, to protect them from destabilisation. This method allowed the pregel to contain an even distribution of hydrophobic material, and allowed reproducible gels to be synthesised as and when required.

4.7.6.2.2 Biphasic skin adhesives containing Lauryl acrylate (LA), Stearyl acrylate (SA) or ESBA as the hydrophobic component

Biphasic hydrogels were synthesised using the compositions listed in table 4.12. Lauryl and stearyl acrylate were selected as alternatives to ESBA. AMO had been established as a good bridging monomer and ensured that the three dimensional hydrophilic matrix possessed good cohesive and adhesive properties.

NaAMPS (% w/w)	AMO (% w/w)	ESBA (% w/w)	LA (% w/w)	SA (% w/w)	Tn 60 (% w/w)
28.0	19.0	5.0	0	0	0.9
28.0	19.0	0	5.0	0	0.9
28.0	19.0	0	0	5.0	0.9

Table 4.12 Biphasic hydrogel compositions containing ESBA, LA or SA as the hydrophobic component

Addition of 5 % w/w of hydrophobic material resulted in similar adhesive properties in the gel containing ESBA, which was at an acceptable level. The structural integrity of these gels was of the same standard as conventional monophasic gels with one advantage, they have the potential to deliver hydrophobic and hydrophilic actives. Monophasic gels are restricted to deliver hydrophilic actives only.

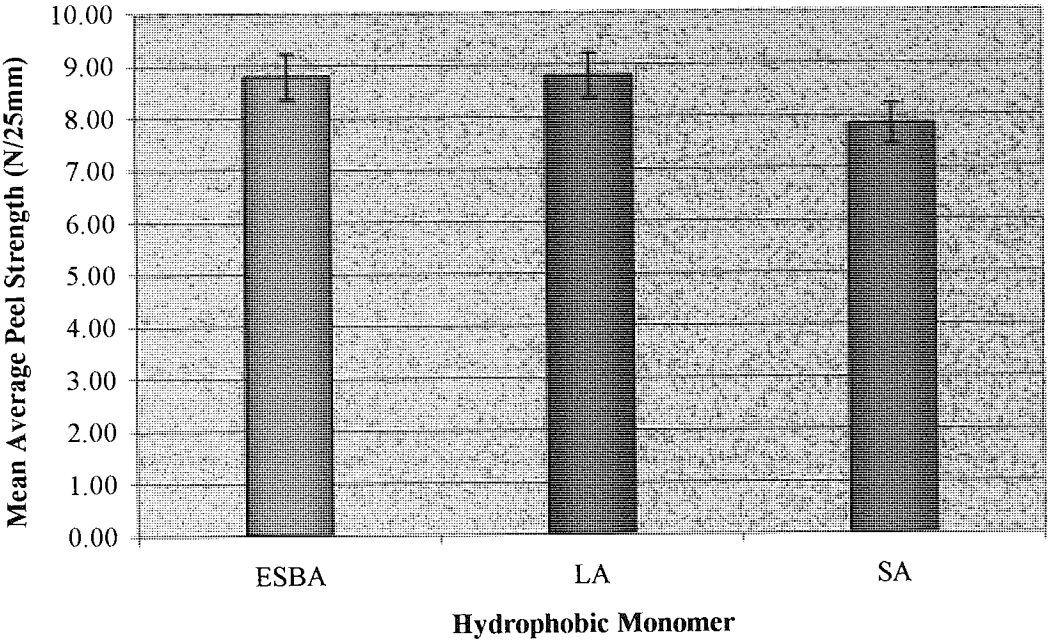


Figure 4.26 Peel strengths of biphasic gels composed of NaAMPS- AMO with either 5 % ESBA, LA or SA as the hydrophobic monomer

4.7.6.2.3 Reduction in the percentage of hydrophobic monomer added

This section investigated the effect of reducing the amount of hydrophobic material on the adhesive properties. Peel tests showed similar results to those obtained in the previous section. A decrease in the amount of hydrophobic material should result in an increase in the adhesive strength. This section illustrates that it is important to decrease the amount of surfactant and a decrease in the hydrophobic monomer, when Tween 60 is incorporated into the gel. The gels synthesised were of acceptable peel strengths but the excess surfactant played a dominant role and interfered with the adhesion of the gel. The gels produced had good cohesive properties and were transparent, which allowed them to be used where the site of attachment must be monitored.

NaAMPS (% w/w)	AMO (% w/w)	ESBA (% w/w)	LA (% w/w)	SA (% w/w)	Tn 60 (% w/w)
29.0	19.0	3.0	0	0	0.9
29.0	19.0	0	3.0	0	0.9
29.0	19.0	0	0	3.0	0.9

Table 4.13 Compositions of biphasic hydrogels containing 3% w/w hydrophobic monomer

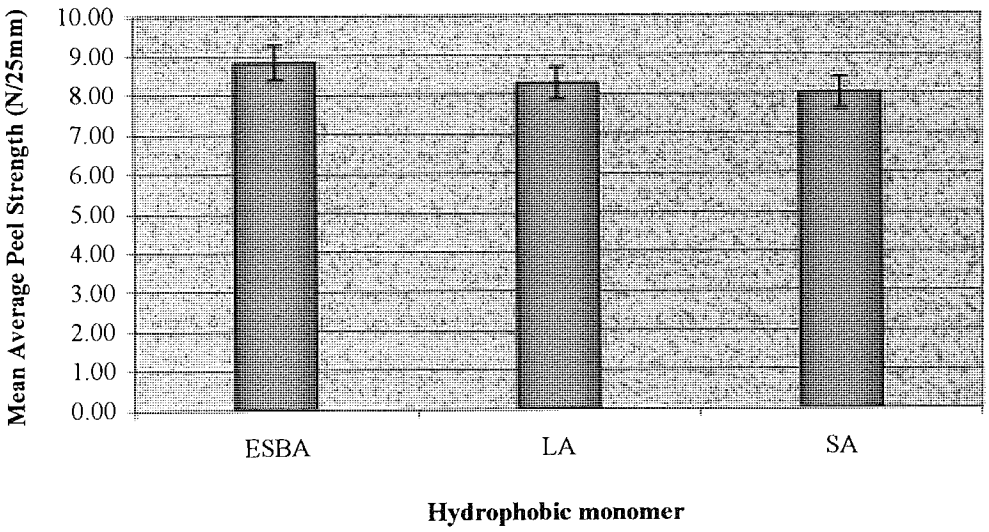


Figure 4.27 Peel tests of biphasic hydrogels containing 3 % w/w hydrophobic monomer

The rheological studies showed that the elastic modulus was greater than the viscous modulus, a prerequisite for viscoelastic skin adhesive hydrogels. This was also verified by the Tan δ value of less than 1. The results obtained at low shear stress showed the ease with which the gel could be attached to the skin. ESBA containing gels were easier to

attach, compared to the other two but overall the viscous modulus complied with the ranges stated in section 2.3.2.1.

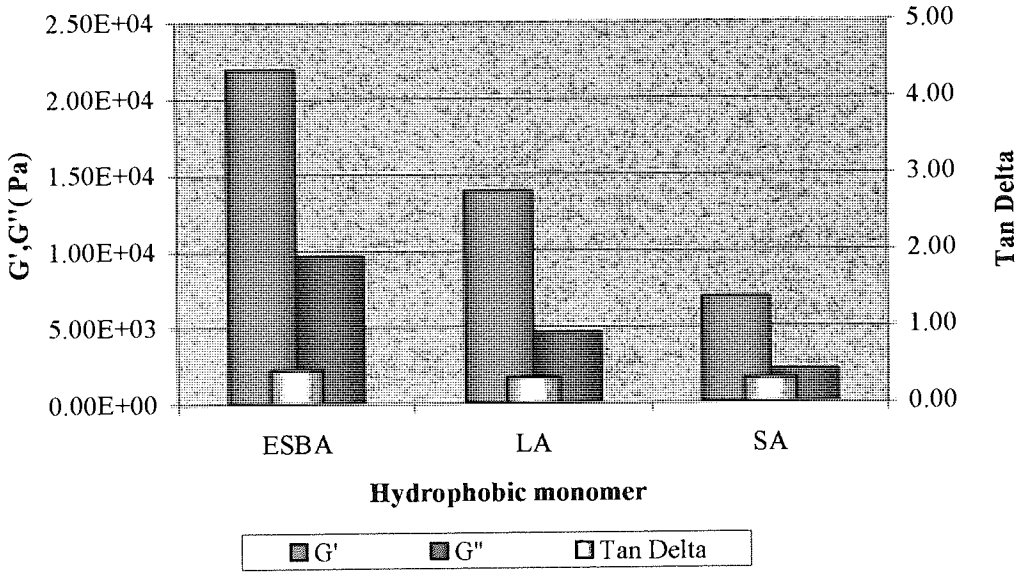


Figure 4.28 Rheological properties of biphasic hydrogels containing 3 % w/w hydrophobic monomer at 1 Hz

The information about the ease of removal of a skin adhesive can be obtained from the data collected at high shear stress. The gels were removed in one piece and no residue was left behind. The data obtained for the elastic moduli of the biphasic polymers were well within the range of 10^3 Pa to 10^5 Pa for a viscoelastic gel. An increase in the shear stress resulted in an increase in the elastic and viscous moduli of the gels. The crosslink density was at an optimum level which ensured that the gel maintained its structural integrity, throughout the test. Cohesive failure would have resulted if the viscous modulus was dominating.

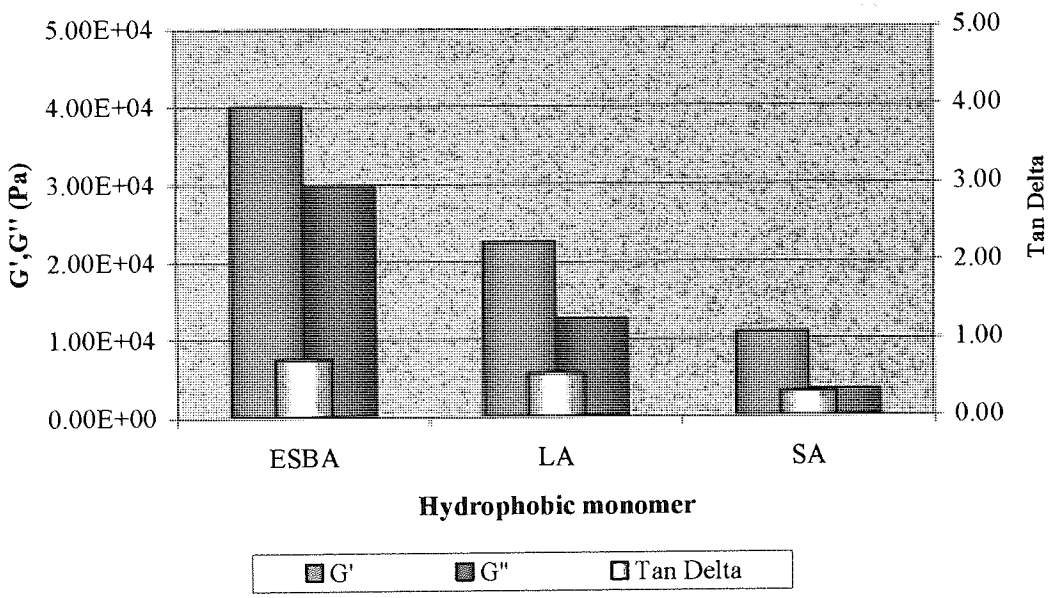


Figure 4.29 Rheological properties of biphasic hydrogels containing 3 % w/w hydrophobic monomer at 10 Hz

4.7.6.2.4 Removal of the hydrophobic component to highlight the properties of the skin adhesive

The hydrophobic component was removed from the biphasic skin adhesive composition to allow the effect of the surfactant Tween 60 upon the hydrophilic polymer matrix to be displayed. As shown in table 4.14 the compositions were for a monophasic gel containing no surfactant, 0.6 % w/w of Tween 60 and 0.9 % w/w of Tween 60. As shown in chapter 3 the gel containing no surfactant yielded the highest peel strength and a similar response was observed for the gel in this section. An increase in the surfactant resulted in a decrease of the peel strength of the gel from the substrate. The gels have an acceptable level of adhesion and the peel strength value at 0.9 % w/w of Tween 60 was reduced by approximately 12 %, when the hydrophobic monomer is incorporated. This value was acceptable when taking into consideration that a gel with a high peel strength is reduced when a surfactant is incorporated.

NaAMPS (% w/w)	AMO (% w/w)	Glycerol (% w/w)	Tn 60 (% w/w)
30	20	28	0.0
30	20	28	0.6
30	20	28	0.9

Table 4.14 Compositions of monophasic gels without the hydrophobic monomer and varying amounts of Tween 60

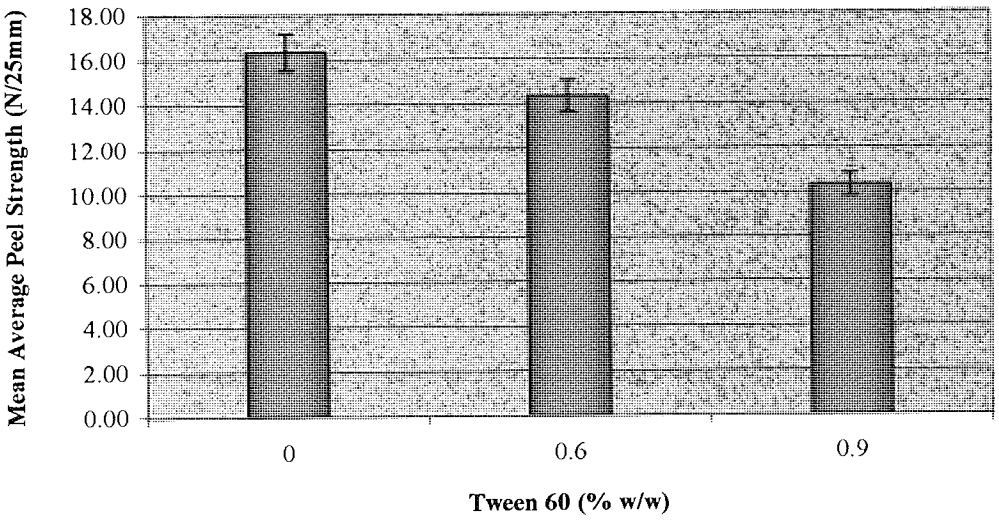


Figure 4.30 Peel strengths of monophasic gel compositions without the hydrophobic monomer and varying amounts of Tween 60

4.7.7 Increasing amount of hydrophobic monomer in a formulation used to synthesise biphasic skin adhesive hydrogels containing Tween 60

Biphasic hydrogels composed of NaAMPS an ionic hydrophilic monomer, AMO a non ionic monomer, glycerol and a hydrophobic monomer ESBA, LA or SA in the presence of a surfactant Tween 60 were synthesised using the compositions in table 4.15. This section investigates the effects of increasing the hydrophobic content of a skin adhesive and aims to establish the amount of hydrophobic material that can be added.

NaAMPS (% w/w)	AMO (% w/w)	ESBA (% w/w)	LA (% w/w)	SA (% w/w)	Tn 60 (% w/w)
28.0	19.0	6.0	0.0	0.0	0.7
28.0	19.0	0.0	6.0	0.0	0.7
28.0	19.0	0.0	0.0	6.0	0.7
27.2	19.0	8.0	0.0	0.0	0.9
27.2	19.0	0.0	8.0	0.0	0.9
27.2	19.0	0.0	0.0	8.0	0.9

Table 4.15 Compositions of biphasic hydrogels containing varying amounts of hydrophobic monomer and a surfactant Tween 60

The pregel formulations were homogenous showing that an adequate amount of surfactant was added. Peel strength results showed that LA gels containing 6 and 8 % w/w of the hydrophobic monomer produced the highest adhesive strength. SA and ESBA containing gels gave similar peel strengths. As the amount of hydrophobic monomer was increased it resulted in the incorporation of less hydrophilic monomer. This contributed to

the reduction in peel strength. The structural integrity was not reduced, however if the percentages of the hydrophobic monomer were increased further and would have resulted in non adhesive gels.

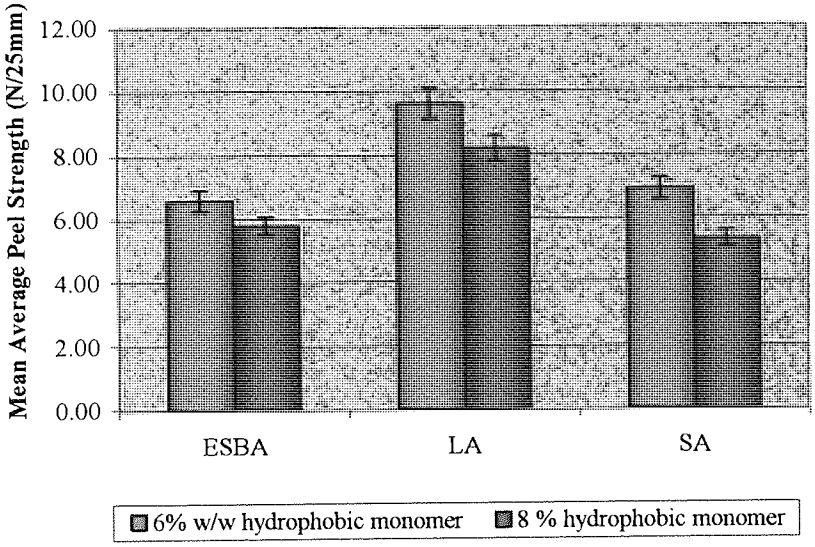


Figure 4.31 Peel strengths of gels containing 6 or 8 % w/w of hydrophobic monomer with Tween 60

Skin adhesives hydrogels are partially hydrated and have the ability to remove interfacial moisture which increases the strength of the adhesive bond. The adhesive and mechanical properties of the gel are important basic requirements for a skin adhesive hydrogel. The top surface of a biphasic gel contains the hydrophobic polymer solubilised within the surfactant micelle. Gels containing 6 % w/w of hydrophobic monomer were stained with a saturated solution of bromopyrogallol red in methanol. They were examined under an optical microscope to investigate the surface of the biphasic hydrogels. For the application of topical delivery it is essential that there is an even distribution of the hydrophobic monomer, otherwise it will result in sections of the skin adhesive delivering different quantities of actives. LA gels presented a well distributed fine phase separation when compared to the gels containing SA or ESBA. The gel containing SA had a good phase separation with hydrophobic phases that can be used. The gel containing ESBA the hydrophobic monomer was not distributed evenly throughout the gel. Both LA and SA gels can be used for the topical delivery of active agents.

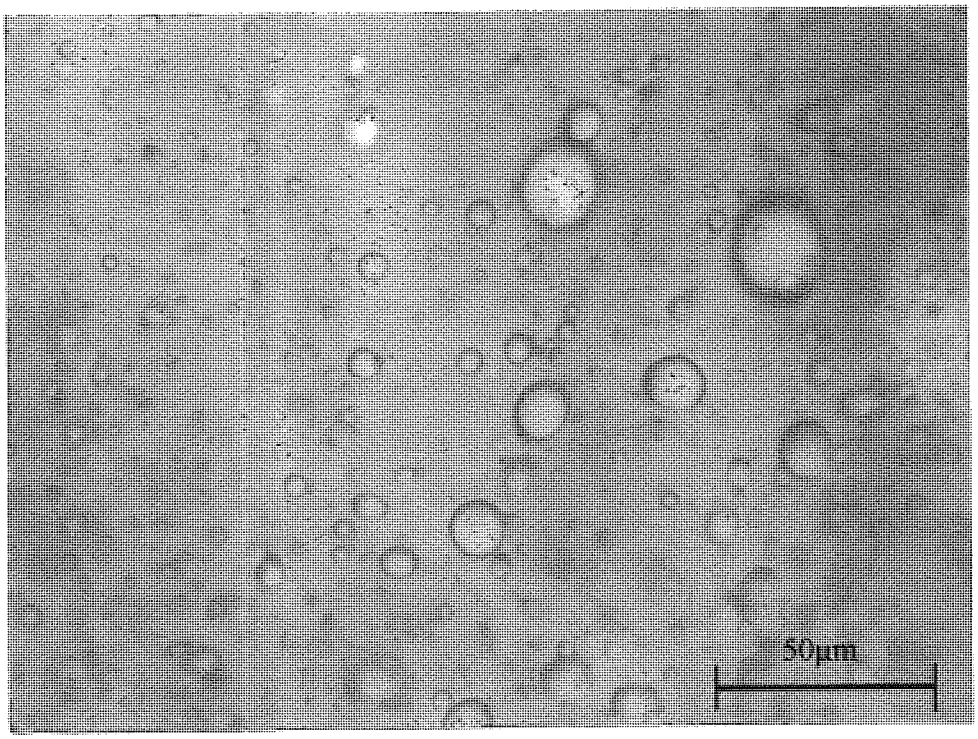


Figure 4.32 Optical micrograph of a 6% w/w ESBA biphasic hydrogel stained with a saturated solution of Bromopyrogallol red in methanol at a magnification of 10/0.25

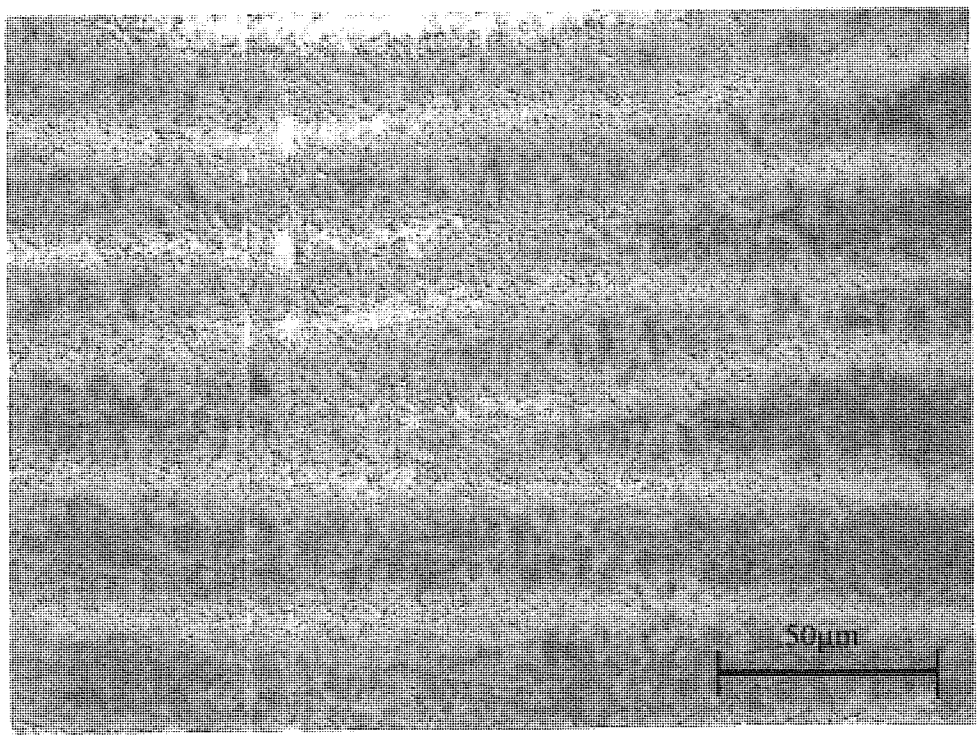


Figure 4.33 Optical micrograph of a 6 % w/w LA biphasic hydrogel stained with a saturated solution of Bromopyrogallol red in methanol at a magnification of 10/0.25

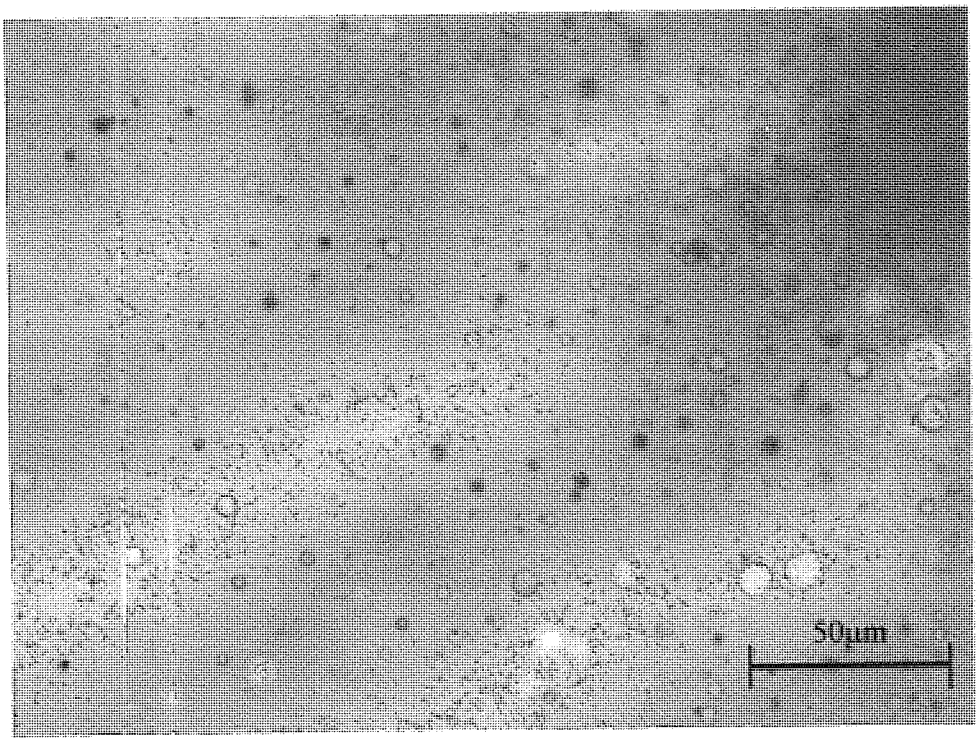


Figure 4.34 Optical micrograph of a 6% w/w SA biphasic hydrogel stained with a saturated solution of Bromopyrogallol red in methanol at a magnification of 10/0.25

4.8 Discussion

Monophasic skin adhesive technology was utilised to enable the development of novel biphasic skin adhesive hydrogels. They contained a hydrophobic polymer distributed within a three dimensional hydrophilic polymer matrix. Due to the limitations placed upon monophasic gels they can only release hydrophilic actives. Biphasic gels were designed to allow the release of both hydrophilic and hydrophobic actives.

Initially, the hydrophobic monomer ESBA was selected due to its low toxicity and pleasant odour which made it easy to work with in a laboratory. This fatty acid ester would not cause skin irritations since this class of lipid naturally occurs within the skin. Its polymerisability was determined with HEMA and N,N DMA. The corresponding copolymers were synthesised as fully hydrated non adhesive hydrogels. A transfer of technology allowed the incorporation of the hydrophobic monomer to a skin adhesive hydrogel.

A suitable bridging monomer was required and therefore N,N DMA, NVP and AMO were investigated. AMO was determined to be more suitable. It possesses three potential sites where hydrogen bonding could occur, compared to N,N DMA and NVP which only have two sites. Also it was polymerisable by UV light. It provided a bridge which brought both the hydrophilic and hydrophobic chemicals together. This type of monomer ensured that phase separation did not occur within the pregel mixture when at an appropriate amount was added.

Surfactants were added to aid the distribution and stability of the hydrophobic monomer within the pregel. Pluronics were not suitable because they were bulky which restricted their mobility within the gels. They also interfered with the adhesive properties of the gel. Ideal surfactants were Tween 20 and 60. They were smaller than the Pluronics and they solubilised the hydrophobic monomer with ease. Elevated quantities of the surfactant did interfere with the adhesive strength of the gel, hence an optimum amount is required which is dependant upon the amount of hydrophobic monomer added.

Alternative hydrophobic monomers butyl acrylate, lauryl acrylate and stearyl acrylate were selected due to their smaller size compared to ESBA. This aided their mobility and their distribution. Due to the potent smell of butyl acrylate it was not incorporated into further compositions. These gels were post cured using gamma radiation which resulted in the residual monomers polymerising and the smell was no longer detectable. The monomer is difficult to work with in the laboratory and therefore on an industrial scale it would be impossible to work with when using UV polymerisation. LA and SA were suitable alternatives and they did not have a potent smell.

Gels produced containing ESBA, LA and SA possessed lower peel strengths than the monophasic monomers which are accounted for by the increase in the hydrophobic content of the gel. Rheological studies showed that the gels possessed the prerequisite structural integrity required for viscoelastic gels. The elastic modulus was greater than the viscous modulus at both low and high shear stresses. The gel maintained its cohesive properties at high shear stresses, showing that it could be removed in one piece without leaving a residue behind.

The phase distribution as shown by optical microscopy highlighted that the bulky ESBA had not been distributed evenly throughout the gel. This would cause problems if it were manufactured on an industrial scale, since each patch would deliver different quantities of hydrophobic and hydrophilic actives. LA showed good hydrophobic phase distribution closely followed by SA containing gels.

Chapter 5

Biphasic Gel Technology: Incorporation of a Commercial Preformed O/W Emulsion

5.1 Introduction

5.1.1 Biphasic Technology containing a preformed O/W Emulsion

Biphasic technology is the term used to describe a hydrogel possessing a two phase system (one hydrophilic component and the other hydrophobic). The previous chapter looks at biphasic gels synthesised by the incorporation of an unsaturated hydrophobic monomer. Table 5.1 shows the main components of a partially hydrated biphasic hydrogel and the contribution that each component gives to the polymer matrix.

Component	Role
Unsaturated Hydrophilic Monomer	Forms the backbone of the 3 dimensional polymer matrix.
Preformed Commercial O/W emulsion	Allows hydrophobic active agents to be dissolved within this domain. They cannot be located within the hydrophilic domain.
Solvent bridging monomer	Links the hydrophilic and hydrophobic monomers together. It contributes to the properties of the gel.
Glycerol	Acts as a humectant by reducing the rate of evaporation of water through hydrogen bonding.
Water	Plasticises the gel allowing it to conform to the site of attachment. Enhances permeability of actives through the matrix.
Surfactant	Added to form micelles, by encapsulating the unsaturated hydrophobic monomer which produces a homogeneous pregel.

Component	Role
Initiator	Required to initiate free radical polymerisation via the formation of active centres and donation of electrons.
Cross linker	Bifunctional monomer/polymer gives the gel its ability to swell without the loss of its structural integrity or the three dimensional matrix.

Table 5.1 Components of partially hydrated biphasic hydrogels containing an O/W emulsion and their roles

5.1.2 Emulsions

An emulsion is defined as an opaque, heterogeneous system of two immiscible liquid phases (oil and water). One of the phases is dispersed in the other microscopically or of colloidal size, which has a typical diameter of 1μm. Two types of simple emulsions exist, either as a water-in-oil (W/O) or oil-in-water (O/W) (figure 5.1), depending upon which phase comprises the drops. These emulsions are very unstable if they are made by agitation, without the presence of a surfactant. Surface active agents are added to protect the newly formed drops from re-coalescence. As described previously an emulsifier with a HLB value within the range of 3 and 6 is useful when a W/O emulsion is required and for an O/W emulsion an emulsifier must possess a HLB value between 8 and 18.

The emulsifier essentially facilitates the formation and aids the stabilisation of the required phase through the combination of surface activity and possible structure formation at the interface. A number of other factors must be taken into consideration when emulsion formation is undertaken, for example the ratio of oil and water, electrolyte concentration, emulsifier concentration, HLB value of the emulsifier and temperature (Tardos T.F, 2005, Farn R., 2006, Binks B.P., 1998, Everett D.H., 1998).

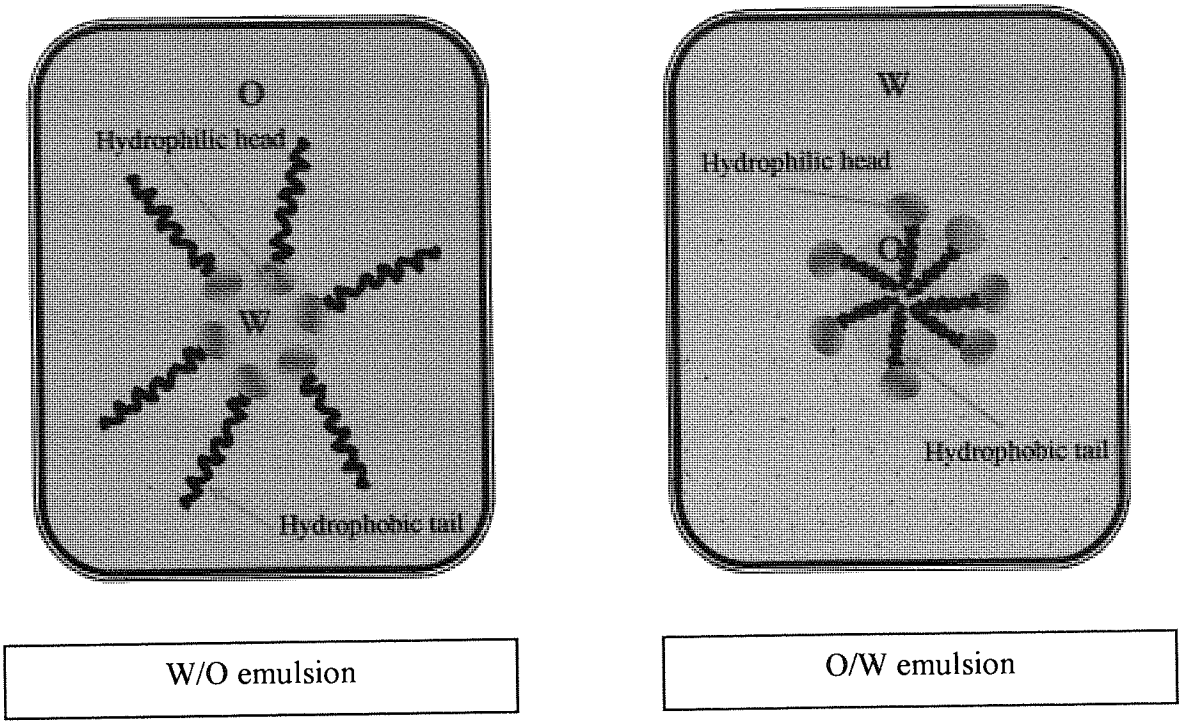


Figure 5.1 Water-in-oil and oil-in-water emulsions

5.1.3 Emulsion polymerisation

The production of latex paints, adhesives, paper coatings and textile finishings are based upon emulsion polymerisation of the homo or copolymers of vinyl acetate. This type of polymerisation is carried out in a reactor which has a mechanical stirrer, a heater and access points, to allow the chemicals to be added as and when required. Two immiscible liquid phases are present in emulsion polymerisation, an aqueous continuous phase (e.g. water) and a non aqueous discontinuous phase consisting of a hydrophobic monomer or polymer. A water soluble thermal initiator (e.g. peroxide or persulfate) was dispersed throughout the aqueous phase. When a sufficient amount of thermal energy was put into the system the chemical decomposed and the initial free radicals were created.

The addition of a surfactant (e.g. sodium lauryl sulfate) to water at its CMC resulted in the formation of micelles, which provided stability for the polymer particles and monomer droplets. Figure 5.2 shows the initial situation where the monomer is

dispersed into small droplets by mixing the chemicals with a mechanical stirrer. The stabilisation was aided by the surfactant. Any remaining surfactant formed micelles with diameters of approximately 10nm. They are substantially smaller when compared to the monomer droplets (1-10μm). Monomer was located within the micelles and also as large droplets, which act as reservoirs. This allows the diffusion of monomer through the water phase into the micelle. From an experimental point of view an in-situ-seed latex situation is achieved by introducing the water, surfactant, a small portion of monomer and part of the initiator, which allows control of the particle formation step and then the remaining monomer and initiator are added after stage 1.

During stage 1 the initiator (I-I) decomposes with heat to form two radicals (2R*) and one of these radicals react with the monomer present in the water phase to form oligomer chains. The oligomers can either be absorbed into a micelle or they can continue to grow and absorb surfactant molecules. In either case, it results in the formation of new polymer and this process continues until no micelles are left and the seed latex has been generated.

During stage 2, monomer migrates from the large monomer droplets through the water which are absorbed by the polymer particle. Polymerisation proceeds mainly in the monomer- swollen polymer particles without the formation of new particles. Monomer consumption is high in this stage and levels are replenished by the continual addition of new monomer from the large droplets. Growing particles are stabilised by adsorption and or grafting of surfactants and colloids onto their surface. The addition of fresh initiator ensures that there is a sufficient supply of free radicals upon decomposition, to allow the polymerisation process to proceed. Addition of the remaining monomer results in polymerisation progressing further with the conversion of residual monomer in the polymer particles. Gradually the rate of polymerisation will slow down and eventually decreases to zero, indicating that no residual monomer remains in the reactor (stage 3) (Billmeyer F.W. Jr, Cowie J.M.G., 1991, 1984, Flory P.J., 1953, Young R.J. et al, 1991).

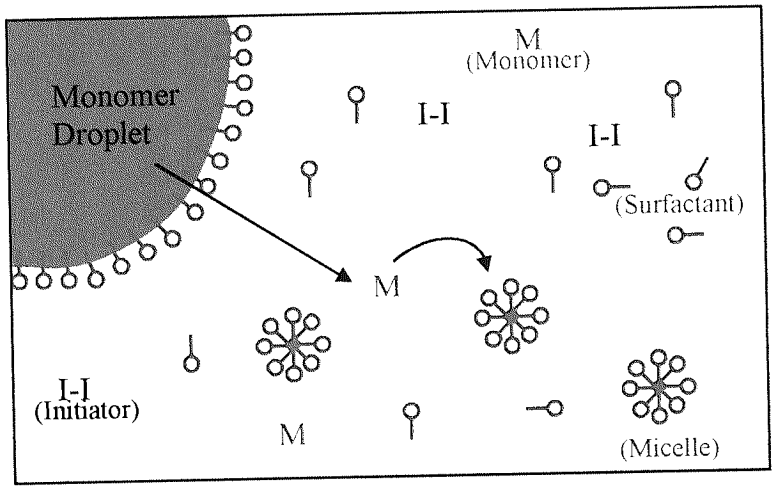


Figure 5.2 Initial situation of emulsion polymerisation

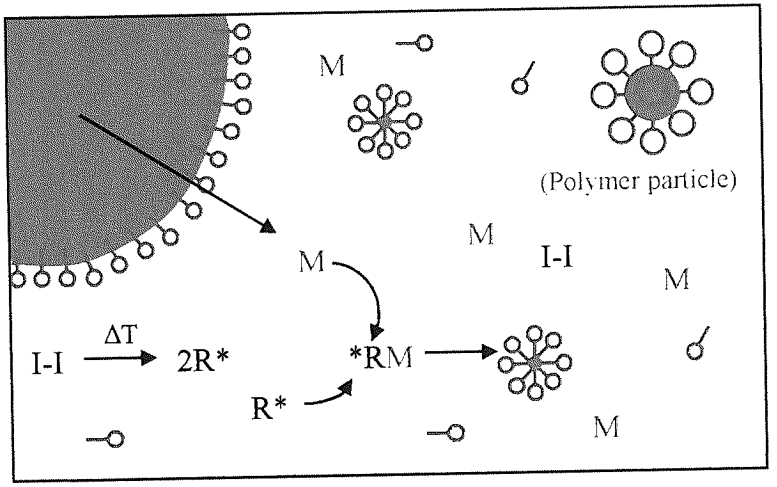


Figure 5.3 Stage 1 of emulsion polymerisation

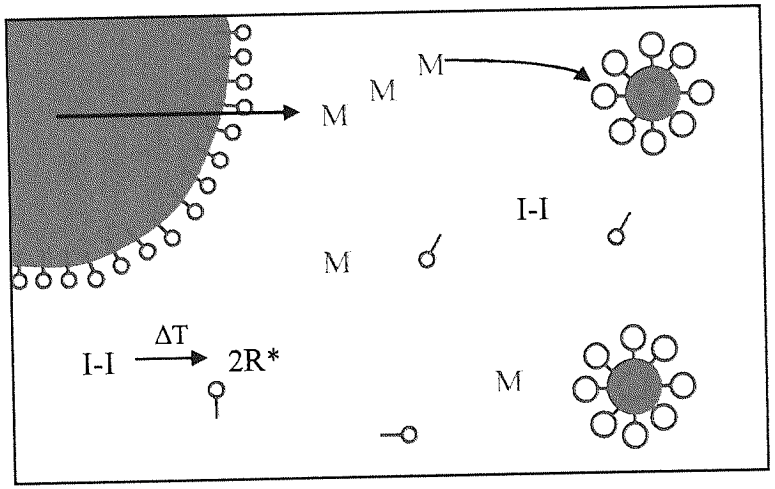


Figure 5.4 Stage 2 of emulsion polymerisation

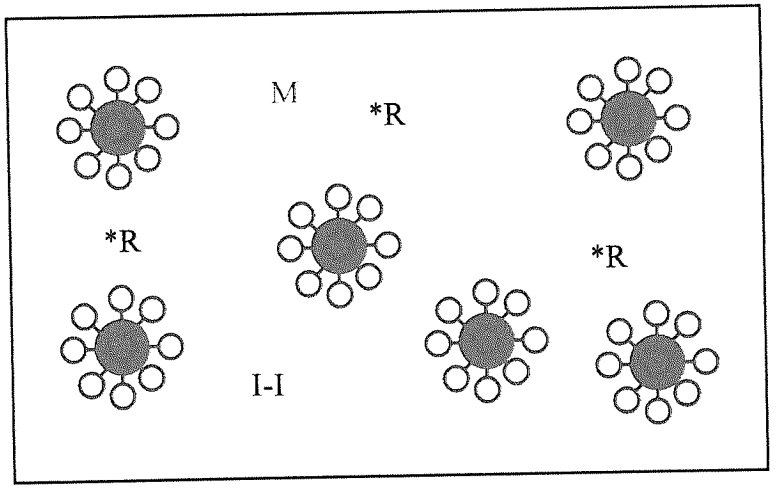


Figure 5.5 Stage 3 of emulsion polymerisation

Two forms of stabilisation prevent the premature coagulation of the latex, electrostatic repulsion and steric stabilisation. They occur in this combination since they compliment each other and optimum results are achieved. The electrostatic repulsion is achieved by the incorporation of an anionic surfactant with negatively charged functional groups located at the polymer/water interface. Hydrophilic groups located at the surface of the polymer particles can impose steric stabilisation. The hydrophilic groups (e.g. non ionic surfactant) strongly attract water. This creates a so called protective water barrier between the particles which prevent coagulation (Binks B.P., 1998, Everett D.H., 1998).

5.2 Aims

Extensive studies have previously been carried out to incorporate an unsaturated hydrophobic monomer into a predominantly hydrophilic pregel. Many problems arise from this situation, in particular the phase stability and distribution throughout the three dimensional polymer matrix. Therefore the focus of this chapter is placed on the incorporation of a commercial preformed O/W emulsion which contains the hydrophobic component.

A wide range of O/W emulsions are commercially available, therefore only a few were selected. It is essential that their compatibility is determined with the standard components used in monophasic pregels. The optimum synthetic conditions required to incorporate an emulsion need to be identified. Structural integrity of the skin adhesive hydrogels must be maintained when incorporating an O/W emulsion. The peel strengths and rheological studies of these gels should be used to determine what effect the emulsion may have on the skin adhesive.

5.3 Results

5.3.1 Incorporation of preformed emulsions as an alternative method of hydrophobic monomer addition

5.3.1.1 A preliminary investigation showing the compatibility of preformed O/W acrylic emulsions with a conventional hydrogel composition

A conventional hydrogel comprises of NaAMPS as the hydrophilic monomer, glycerol as a humectant and water as a plasticiser. Incorporation of an emulsion will not occur by the simple addition to a NaAMPS composition. This results in precipitation of the emulsion forming a solid coagulated mass of hydrophobic monomer or smaller sized precipitate throughout the solution. This showed that the emulsion had destabilised due to the presence of the ionic monomer. The presence of the NaAMPS resulted in the destabilisation and agglomeration when added at high concentrations. The change in the environment also plays a role. Adding the two solutions at room temperature also resulted in coagulation of the polymer. AMO was added to the preformed O/W emulsion to ensure that it was located around the latex particles to increase the hydrophilicity around the particle. They strongly attract water, creating a protective water barrier between the particles which prevent coagulation. The addition of glycerol aided this process. NaAMPS was added slowly to the emulsion to ensure that the AMO and glycerol were not removed from their positions. The speed of mixing was important, since an increase in the mechanical energy resulted in the destabilisation of the emulsions. The temperature at which these experiments were conducted also played a fundamental role. If it were carried out at room temperature and depending upon the amount of emulsion added, it did not form a homogenous solution with the pregel components. At high temperatures for example 70°C, an excessive amount of thermal energy was introduced to the system, causing destabilisation. The optimum temperature used for all experiments was 50°C with mixing at 100 revs/ min. This ensured that the emulsion did not destabilise.

5.3.1.2 Preparation of skin adhesive hydrogels containing 5 % / 10 % w/w of O/W emulsions

Gels were prepared using a similar method to when incorporating a hydrophobic monomer. The emulsion was kept in a separate sample vial to the NaAMPS which reduced the risk of destabilisation occurring. AMO and glycerol were added to the emulsion which acted as a barrier for latex particles when the anionic monomer was added at a later stage. The NaAMPS was heated to ensure that a homogenous solution was formed with the emulsion. 0.20 % w/w of Irgacure 184 and Ebacryl II were used as the initiator and crosslinking system at a 3:10 ratio respectively. 28.8 % w/w of glycerol and 24.5 % w/w of water were added to each formulation displayed in table 5.2.

NaAMPS (% w/w)	**AMO (% w/w)**	**Tn 60 (% w/w)**	**DM137 (% w/w)**	**Flexbond 150 (% w/w)**	**Texicryl 13056WB (% w/w)**
34.0	6.7	1.0	5.0	0.0	0.0
34.0	6.7	1.0	0.0	5.0	0.0
34.0	6.7	1.0	0.0	0.0	5.0
34.0	6.7	1.0	10.0	0.0	0.0
34.0	6.7	1.0	0.0	10.0	0.0
34.0	6.7	1.0	0.0	0.0	10.0

Table 5.2 Biphasic skin adhesives compositions containing 5% or 10 % w/w O/W emulsions

The compositions shown in table 5.2 involved the incorporation of three different types of O/W emulsions, DM137 composed of poly (ethylene-co-vinyl acetate), Flexbond 150

contained poly (dioctyl maleate-co-vinyl acetate) and Texicryl 13056 WB was an acrylic based emulsion. This section highlights that it is possible to incorporate a preformed emulsion into a monophasic skin adhesive without it resulting in destabilisation. A non ionic surfactant, Tween 60 was added at 1.0 % w/w to ensure that the emulsion did not destabilise.

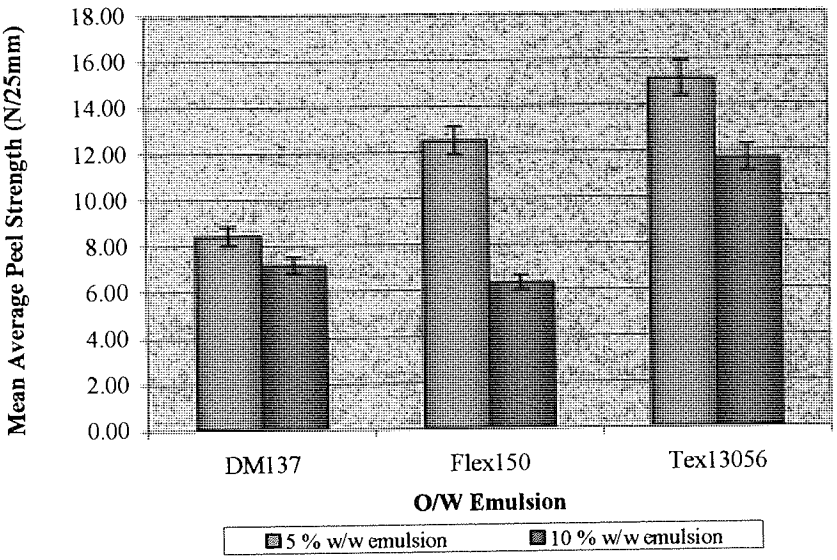


Figure 5.6 Peel strengths of biphasic skin adhesives compositions containing 5% or 10 % w/w O/W emulsion

The peel strengths showed that these gels possessed good adhesive strength. They are usually compromised when the hydrophobic component is increased within a predominantly hydrophilic matrix. The emulsions incorporated had different degrees of hydrophobicity. Texicryl 13056WB was the least hydrophobic and DM137 the most hydrophobic emulsion from those selected. The peel strengths of the gels containing 5% w/w emulsion highlighted that those containing Texicryl 13056 WB had a stronger adhesive bond compared to Flexbond 150 or DM137. An increase in the amount of the O/W resulted in a decrease of adhesive strength. All of these gels possessed good cohesive strength which led to an acceptable level of structural integrity. Gels containing 5 % w/w of O/W emulsion were semi opaque, whereas 10 % w/w of O/W emulsion gels were opaque. The quantity of the hydrophobic component determined whether or not the

gel would be suitable for certain applications. These gels contained similar amounts of hydrophobic monomer to those composed in previous sections. The addition of an O/W emulsion does not interfere with the hydrophilic matrix to the same extent as ESBA, LA or SA.

5.3.1.3 Preparation of skin adhesive hydrogels containing 25 % w/w of O/W emulsions

Gels containing ESBA, LA and SA were synthesised and due to the limitations they imposed, only 8 % w/w of the hydrophobic monomer was incorporated into the hydrogel matrix. The compositions shown in table 5.3 involved the incorporation of 25 % w/w of an O/W emulsion. 28.7% w/w of glycerol and 23.0% w/w of water were added to each gel. All of the gels were opaque and possessed low adhesive strength. Gels produced had good cohesive strength and the structural integrity had not been compromised.

NaAMPS (% w/w)	**AMO (% w/w)**	**Tn 60 (% w/w)**	**DM137 (% w/w)**	**Flexbond 150 (% w/w)**	**Texicryl 13056WB (% w/w)**
32.0	6.2	1.0	25.0	0.0	0.0
32.0	6.2	1.0	0.0	25.0	0.0
32.0	6.2	1.0	0.0	0.0	25.0

Table 5.3 Biphasic skin adhesives compositions containing 25 % w/w O/W emulsions

From a formulatory perspective, the ease of incorporation differed for the O/W emulsions added. Flexbond 150 was incorporated with more ease than Texicryl 13056WB which required a great deal of care. If the NaAMPS was added too quickly, it resulted in the coagulation of the O/W emulsion.

5.3.1.4 Preparation of biphasic skin adhesive hydrogels without the presence of a bridging monomer

This section highlights the importance of incorporating a non ionic bridging monomer. Gels were synthesised with 4 % w/w of emulsion. When attempts were made to incorporate larger quantities of emulsion it resulted in its destabilisation. Glycerol had an identical role to that of AMO. Its incorporation resulted in a hydrophilic barrier between the hydrophilic groups which attracted the water, creating a protective barrier preventing coagulation.

NaAMPS (% w/w)	**Glycerol (% w/w)**	**H_2O (% w/w)**	**DM137 (% w/w)**	**Flexbond 150 (% w/w)**	**Texicryl 13056WB (% w/w)**	**Acrylic acid (% w/w)**
40.0	28.0	28.0	4.0	0.0	0.0	0.0
40.0	28.0	28.0	0.0	4.0	0.0	0.0
40.0	28.0	28.0	0.0	0.0	4.0	0.0
40.0	28.0	28.0	4.0	0.0	0.0	2.8
40.0	28.0	28.0	0.0	4.0	0.0	2.8
40.0	28.0	28.0	0.0	0.0	4.0	2.8

Table 5.4 Compositions of biphasic gels containing preformed emulsions and an adhesivity enhancing chemical

AMO containing gels have higher peel strengths as determined in previous sections. These gels yielded low values. However, the adhesion enhancing chemical, acrylic acid, was added to ensure that it was compatible with the O/W emulsions. It did not destabilise it, which can occur when the pH of the solution is altered.

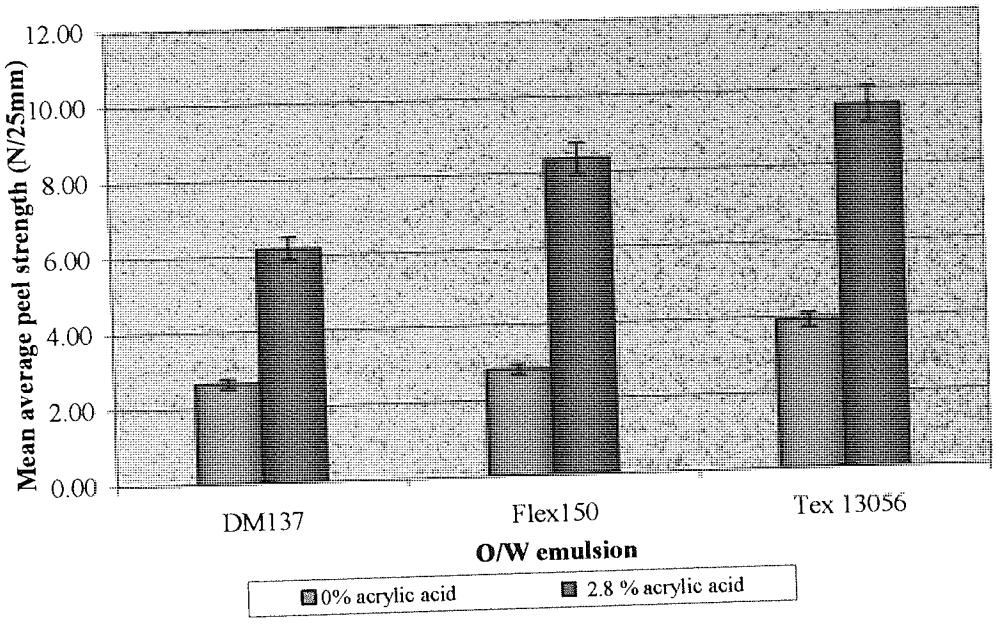


Figure 5.7 Biphasic hydrogels containing O/W emulsions and an adhesivity enhancing chemical

The addition of 2.8 % w/w acrylic acid was an adequate quantity. This resulted in the peel strength approximately doubling, when compared to those gels containing no adhesivity enhancer. The acrylic acid allowed disregarded compositions, due to very low peel strengths, to be made applicable. The water binding potential within the gel was increased and the potential to remove interfacial moisture was increased. This resulted in gels with higher peel strengths.

5.3.1.5 Investigating the effect of incorporating low amounts of DM137 or Flexbond 150 O/W emulsions in biphasic skin adhesive hydrogels

This section investigates the effects of increasing the quantity of the O/W emulsion upon the peel strength. DM137 and Flexbond 150 were selected due to their ease of incorporation into the pregel formulations.

NaAMPS (% w/w)	AMO (% w/w)	Glycerol (% w/w)	H_2O (% w/w)	DM137 (% w/w)	Flexbond 150 (% w/w)
22.0	28.0	35.0	15.0	1.0	0.0
22.0	28.0	35.0	15.0	2.0	0.0
22.0	28.0	35.0	15.0	3.0	0.0
22.0	28.0	35.0	15.0	4.0	0.0
22.0	28.0	35.0	15.0	5.0	0.0
22.0	28.0	35.0	15.0	6.0	0.0
22.0	28.0	35.0	15.0	0.0	1.0
22.0	28.0	35.0	15.0	0.0	2.0
22.0	28.0	35.0	15.0	0.0	3.0
22.0	28.0	35.0	15.0	0.0	4.0
22.0	28.0	35.0	15.0	0.0	5.0
22.0	28.0	35.0	15.0	0.0	6.0

Table 5.5 Compositions of biphasic gels containing varying amounts of the preformed O/W emulsions DM137 and Flexbond 150

The gel containing 1.0 % w/w of DM137 yielded a higher peel strength than the gel containing the same quantity of Flexbond 150. An increase in the amount of DM137 resulted in the reduction of the peel strength. This accounted for the increase in the hydrophobic content, which reduced the strength of the adhesive bond. Flexbond 150 contains a less hydrophobic polymer. The hydrophilic interactions made this emulsion more compatible within the hydrophilic matrix. An increase in the amount of this emulsion increased the peel strength for gels containing up to 4% w/w emulsion. After this point the peel strength decreases. A certain degree of hydrophobicity within a skin adhesive is required in order to achieve a good adhesive bond.

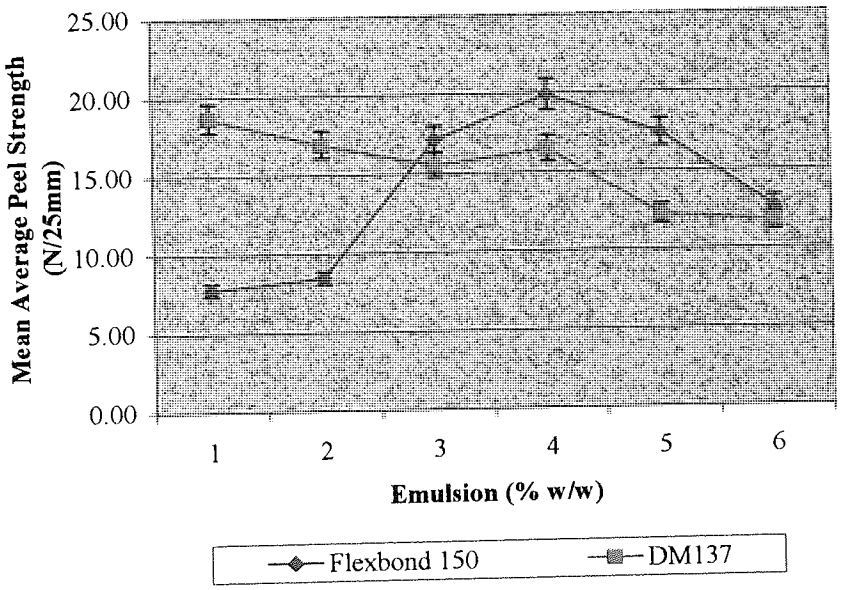


Figure 5.8 Peel strengths of biphasic gels containing varying amounts of the preformed O/W emulsions DM137 and Flexbond 150

All of these gels maintained their structural integrity and had good cohesive strength. Gels containing 1-4 % w/w of the O/W emulsions were transparent and provided a range of peel strengths. The application dictates the peel strength required. It can be altered by incorporating the appropriate quantity and type of an O/W emulsion.

5.3.2 Rheological Comparison of gels containing different emulsions

The incorporation of an O/W emulsion results in an increase in the cohesive properties and adhesive strength, when compared to gels containing ESBA, LA or SA as the hydrophobic monomer. Gels containing 6 % w/w of an O/W emulsion were incorporated into the compositions shown in table 5.6. The amount of glycerol and water added to each gel were 35.0 % w/w and 15.0 % w/w respectively.

NaAMPS (% w/w)	AMO (% w/w)	Acronal (% w/w)	Flexbond 150 (% w/w)	DM137 (% w/w)	Texicryl 13056 (% w/w)
22.0	28.0	0.0	0.0	0.0	0.0
22.0	28.0	6.0	0.0	0.0	0.0
22.0	28.0	0.0	6.0	0.0	0.0
22.0	28.0	0.0	0.0	6.0	0.0
22.0	28.0	0.0	0.0	0.0	6.0

Table 5.6 Compositions of biphasic hydrogels containing 6 % of different O/W emulsion

The rheological properties were studied to establish the effects of the elastic and viscous moduli when O/W emulsions are incorporated. All of the gels were compared to the corresponding monophasic gel containing no emulsion. Gels containing O/W emulsions possessed reduced elastic and viscous moduli at both low and high shear stresses. The restictions imposed by the increase in the hydrophobic content were accountable. The values were still within the ranges stipulated for viscoelastic gels as stated in section 2.3.2.1. The tan δ values were below 1, confirming that the elastic component was greater than the viscous. Gels containing Acronal and Texicryl 13056WB give similar elastic and

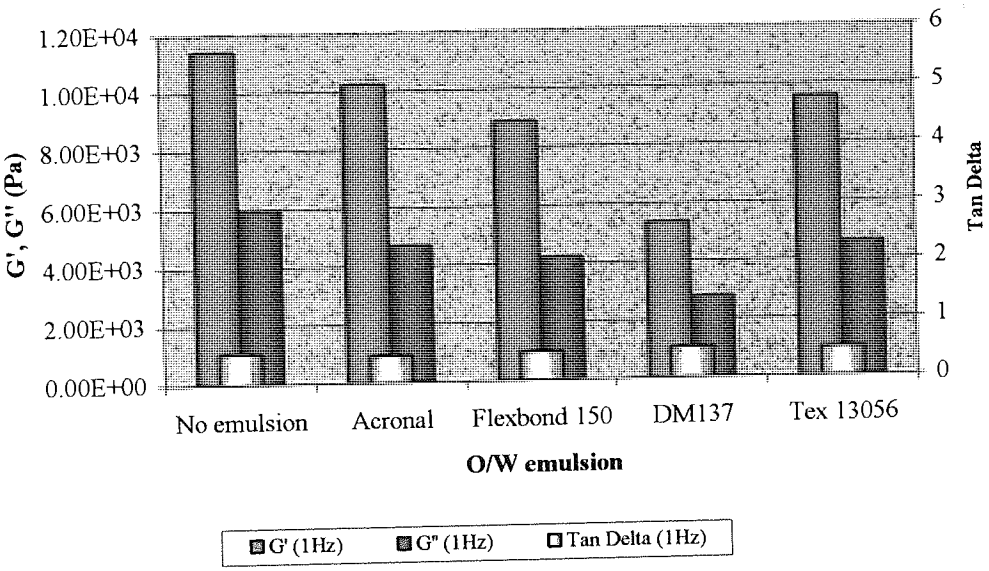


Figure 5.9 Rheological behaviour of biphasic hydrogels containing 6 % O/W emulsion at 1Hz

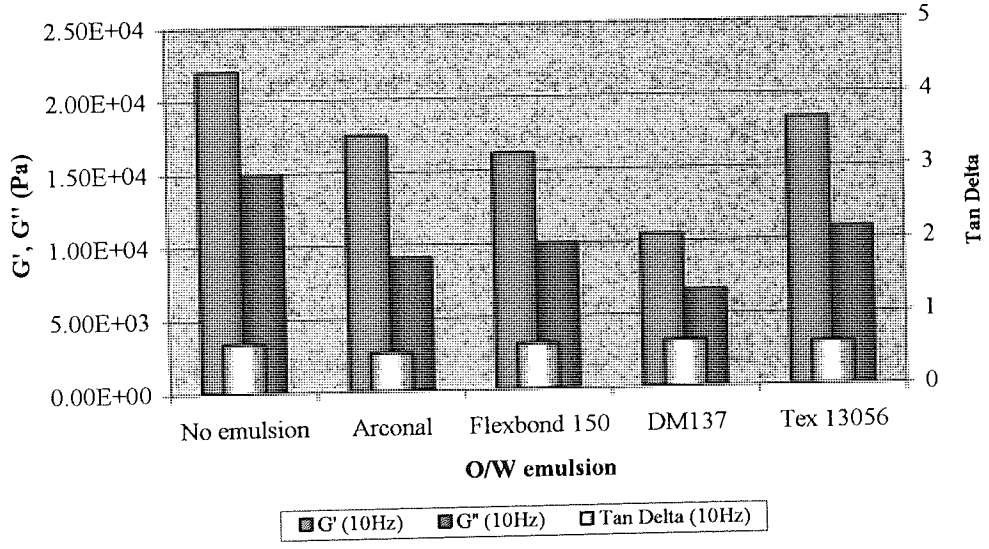


Figure 5.10 Rheological behaviour of biphasic hydrogels containing 6 % O/W emulsion at 10Hz

The ease with which a gel is applied to the skin is determined by the viscous moduli at a low shear stress. The gel containing DM137 yielded the lowest value. It could not flow as much as the other gels, but was still within the acceptable range for the viscous modulus. The elastic moduli at high shear stress were investigated to ensure that the structural integrity was maintained and that the gel could be removed without leaving a residue. Gels containing Acronal, Flexbond 150 and Texicryl 13056 yielded similar values, highlighting that although they possess different chemical structures, they behaved in a similar manner within the hydrophilic polymer matrix. All of these gels could be used to deliver active agents as shown in the following chapters.

5.3.3 Incorporation of Flexbond 150 or DM137 O/W emulsions to a non ionic monomer based composition

As shown in previous sections AMO is an ideal non ionic monomer that is highly compatible with hydrophobic monomers and O/W emulsions. Experimental work carried out in section 3.6.8 showed that the incorporation of a viscosity modifier increased the adhesive strength of the hydrogel. Flexbond 150 and DM137 were selected due to the ease with which they could be incorporated. Gels containing non ionic polymers have a lower degree of swell when compared to those containing polyNaAMPS. It was important to investigate the compatibility of this type of gel with the emulsion technology where swelling must be minimised.

5.3.3.1 Varying the ratio of Flexbond 150 in biphasic compositions containing a non ionic hydrophilic monomer

Table 5.7 highlights the compositions used to synthesise the gels in this section. In addition to PQ4, another viscosity modifier was added to the gels to highlight the effect that this polymer had on the adhesion of the gel. PQ4 or PQ10 were dissolved in water to which AMO and glycerol were added. The emulsion was incorporated into the pregel formulation with ease, compared to the biphasic gels containing NaAMPS.

AMO (% w/w)	Glycerol (% w/w)	H_2O (% w/w)	Flexbond 150 (% w/w)	PQ4 (% w/w)	PQ10 (% w/w)
56.0	28.0	16.0	1.0	0.3	0.0
56.0	28.0	16.0	2.0	0.3	0.0
56.0	28.0	16.0	3.0	0.3	0.0
56.0	28.0	16.0	4.0	0.3	0.0
56.0	28.0	16.0	1.0	0.0	0.3
56.0	28.0	16.0	2.0	0.0	0.3
56.0	28.0	16.0	3.0	0.0	0.3
56.0	28.0	16.0	4.0	0.0	0.3

Table 5.7 Biphasic compositions containing a non ionic hydrophilic monomer with varying amounts of Flexbond 150

In general, gels containing PQ10 gave lower peel strengths compared to their counterparts containing PQ4. The hydrophobicity of PQ10 is accountable and it allows a range of gels to be synthesised, with varying peel strengths, when Flexbond 150 was added.

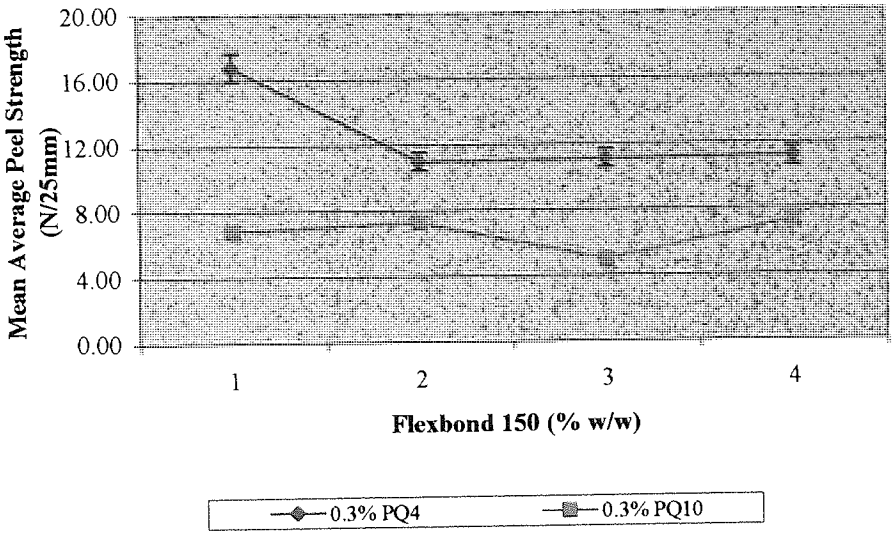


Figure 5.11 Peel strengths of biphasic compositions containing a non ionic hydrophilic monomer with varying amounts of Flexbond 150

5.3.3.2 Varying the ratio of DM137 in biphasic compositions containing a non ionic hydrophilic monomer

Gels synthesised in this section were similar to those in 5.3.3.1. The O/W emulsion DM137 was added to the formulation. Investigations carried out in earlier chapters showed that DM137 yielded gels with lower peel strengths when compared to Flexbond 150. It was compatible with the other components of the pregel composition and when it was incorporated it was not destabilised. An increase in the hydrophobic content resulted in a decrease of the peel strength for gels containing PQ4 and PQ10. The viscosity modifier PQ10 is more hydrophobic than PQ4, which results in a decrease of the peel strength. These gels have adequate to low peel strengths. Gels can be synthesised for the required application, without having to make dramatic changes to the formulation.

AMO (% w/w)	Glycerol (% w/w)	H_2O (% w/w)	DM137 (% w/w)	PQ4 (% w/w)	PQ10 (% w/w)
56.0	28.0	16.0	1.0	0.3	0.0
56.0	28.0	16.0	2.0	0.3	0.0
56.0	28.0	16.0	3.0	0.3	0.0
56.0	28.0	16.0	4.0	0.3	0.0
56.0	28.0	16.0	1.0	0.0	0.3
56.0	28.0	16.0	2.0	0.0	0.3
56.0	28.0	16.0	3.0	0.0	0.3
56.0	28.0	16.0	4.0	0.0	0.3

Table 5.8 Biphasic compositions containing a non ionic hydrophilic monomer with varying amounts of DM137

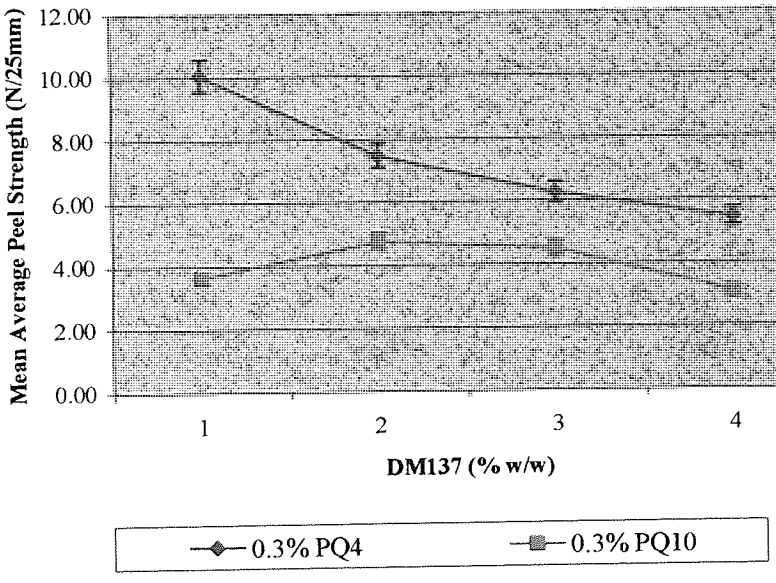


Figure 5.12 Peel strengths of biphasic compositions containing a non ionic hydrophilic monomer with varying amounts of DM137

5.4 Discussion

A hydrophobic component was added in the form of a preformed O/W emulsion, to a predominantly hydrophilic pregel. Incorporation of an unsaturated hydrophobic monomer required specialist preparation to ensure that a homogenous pregel solution was achieved. Preformed emulsions could be added since the hydrophobic component was predispersed and stabilised throughout the water phase.

Direct addition of the emulsion to a NaAMPS pregel led to its destabilisation and agglomeration. Addition at room temperature resulted in this phenomenon occurring, therefore another method was required. AMO was added to the preformed O/W emulsion allowing it to locate itself around the latex particles. This increased the hydrophilicity around the structure which strongly attracted water, creating a protective water barrier between them. Coagulation was prevented by this process.

The addition of glycerol aided this process and allowed the NaAMPS to be added slowly, ensuring that the AMO was not displaced. If the speed of mixing was in excess of 250 revs per min using this system it resulted in destabilisation of this system. At a temperature of 70°C, the stability of the emulsion was compromised. Optimum conditions for the preparation of these types of pregels were deciphered from these preliminary studies. They should be heated to 50°C with mixing at 100 revs/min, to ensure that a homogeneous pregel was achieved.

Incorporation of 5 % w/w of DM137, Flexbond 150 or Texicryl 13056WB to a monophasic pregel resulted in the adhesion of the gels increasing, when compared to those containing no O/W emulsion. The cohesive and adhesive strength increased, when an emulsion was added. The hydrophobicity at the surface of the gel and interaction of the hydrophilic component of the polymer with the aqueous pregel environment were enhanced. Gels containing 5 % w/w of Texicryl 13056WB O/W emulsion had a stronger adhesive bond when compared to Flexbond 150 or DM137. Different types of emulsions behave in accordance with the environment in which they are placed.

The incorporation of 25 % w/w of an O/W emulsion was regarded as being a high level. It resulted in opaque gels possessing a lower adhesive strength, when compared to gels containing 10 % w/w. The gels possessed good cohesive strength and their structural integrity had not been compromised. Lower quantities of the emulsion interacted with the components present in the pregel enhancing the physical properties of the gel. However, amounts added in excess of 10 % w/w restricted molecular motions, which reduced the potential skin contact in particular the adhesive bond between the substrate and the gel.

Flexbond 150 was incorporated with ease from a synthetic perspective, when compared to Texicryl 13056WB. The application determines the level of adhesion required by a gel to fulfill its role. However, 4 % w/w of emulsion can be used in conjunction with 2.8 % w/w of acrylic acid which approximately doubles the peel strength of these gels. The water binding potential within the gel is increased by the interactions between the acrylic acid and hydrophilic components, through hydrogen bonding. This allowed rotation of polymer chains increasing intermolecular interaction for example between the sulphonate and amide group on two different NaAMPS molecules.

As the quantity of DM137 was increased the peel strength decreased. No more than 4 % w/w of Flexbond 150 increased the peel strength. The later was less hydrophobic than DM137 and therefore more hydrophilic interactions occurred increasing its compatibility within the three dimensional hydrophilic polymer matrix. Gels containing between 1 and 4 % w/w of emulsion were transparent making them appropriate for an application where the underlying skin should be visible.

Rheological studies of the hydrogels containing O/W emulsions showed that the elastic and viscous moduli were lower than those results obtained for a monophasic gel at low and high shear stresses. An increase in the hydrophobic content affected the mechanical properties of the gel due to the restrictions imposed by them. Tan δ values for these gels were below 1 highlighting that despite having lower elastic and viscous moduli they were classified as viscoelastic materials.

Hydrogels containing 6 % w/w of Acronal, Texicryl 13056WB or Flexbond 150 gave similar elastic and viscous moduli at low and high shear stresses. Acronal was the most difficult O/W emulsion to incorporate into a pregel, its stability was compromised. The NaAMPS monomer was replaced with AMO as the primary unsaturated hydrophilic monomer. This non ionic monomer was highly compatible with the O/W emulsions.

Non ionic gels containing 0.3 % w/w of PQ4 and Flexbond 150 or DM137 gave higher peel strengths than those containing 0.3 % w/w of PQ10. The polymers PQ4 and PQ10 were used as viscosity modifiers, however they possessed another role as adhesivity enhancers, when used at low concentrations of 0.3 % w/w. PQ10 was more hydrophobic which reduced the adhesive strength. The range of gels synthesised could be used for a variety of applications and have the potential to release actives.

Chapter 6

Incorporation of active agents to skin adhesive hydrogels

6. Introduction

6.1 Stratum corneum - normal and low levels of moisture

The stratum corneum is comprised of tightly packed specialised cells, known as the corneocytes (bricks), bound together with lipids (mortar). As shown in figure 6.1 natural oil sebum is present on the surface of skin to reduce the amount of water loss. Natural moisturising factors (NMFs) are located within the corneocytes principally to retain and attract water. These water soluble substances play a major role in the regulation of water and also have a protective function in the skin (Antczak S., 2001, Loden M., 2000).

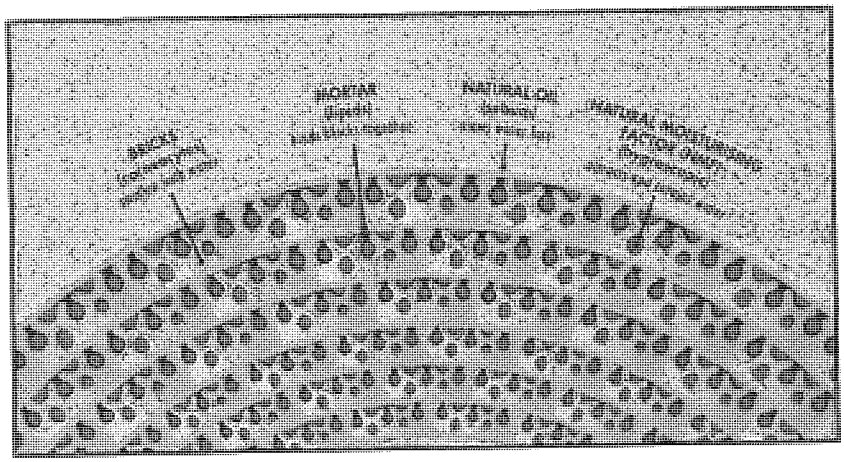


Figure 6.1 Normal level of moisture – Structure of the stratum corneum bricks and mortar depiction

A reduction in the concentration of NMF levels in the corneocytes result in the loss of water from the skin's surface. Low levels of moisture are taken as being lower than 10%. The skin contains less NMF which holds water in the corneocytes (bricks). Unfavorable properties of the skin for example tightness occur, the decrease in the moisture level is not counterbalanced, the corneocytes degrade, shrink and crack. Eventually the protective lipid barrier breaks down between the corneocytes and gaps begin to appear leaving the skin open to attack from bacteria and allergens (figure 6.2).

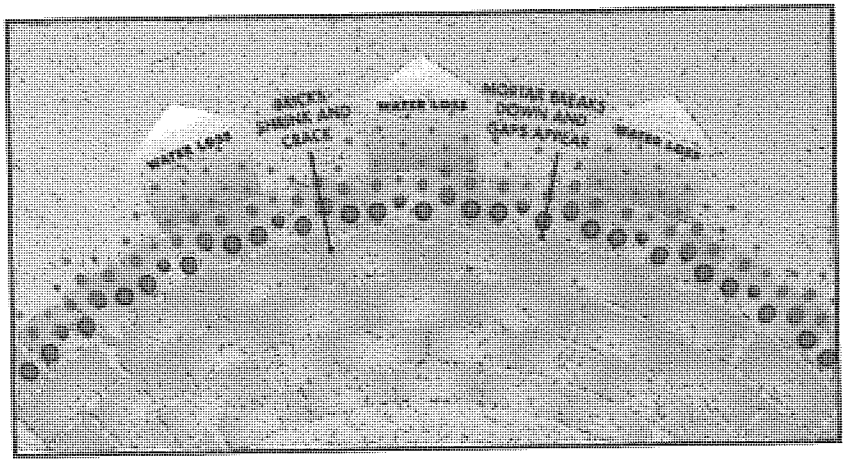


Figure 6.2 Low level of moisture - Structure of the stratum corneum

Moisturisation of the skin involves a four step process which starts with repair of the skin barrier. Step two involves the increase in the water content of the skin and it takes time for the human body to replenish the supplies of NMFs. The reduction of the transepidermal water loss (TEWL) and also the restoration of the lipid barrier contribute to the process. To ensure that the skin is not adversely damaged, dry skin is combated by the introduction of external moisturisers which are applied to the outer surface of the skin.

A number of factors can contribute to dry skin including the sun, extreme cold weather, old age, excessive amounts of bathing. There are cases where this type of condition arises from a combination of factors. All individuals have unique skin and therefore different conditions can have different effects. In general, dry skin can be treated with commercially available moisturisers. However, in extreme cases specialist moisturisers are used to treat specific conditions.

6.2 Commercial moisturisers

An array of moisturising lotions and creams are widely available, to address problems arising from the inadequate hydration of skin. In essence, they provide a protective film which reduces the rate of evaporation of skin moisture also known as the transepidermal water loss (TEWL), whilst improving the properties of the skin. Water originates in the deeper epidermal layers, migrates upward to hydrate cells in the stratum corneum and is eventually lost from the skin by the process of evaporation. Occulsives are components that physically block the TEWL from the stratum corneum. The most effective known occlusive is petrolatum used at a minimum concentration of 5%. Other alternatives include lanolin which is a complex structure of esters, diesters and hydroxyl esters of high molecular weight (Antczak S., 2001).

Humectants improve the hydration of the skin when applied topically because they attract water. Only transepidermal water is drawn to the skin and not atmospheric, therefore continued evaporation can take place which exacerbates dryness. Glycerin, urea, alpha hydroxyl acids are a few examples but the major NMF known is 2-pyrrolidone carboxylic acid (PCA). The incorporation of these humectants are carefully considered, for example low concentrations can be advantageous and give the effect required but at higher concentrations it can cause irritation. For example a 10% concentration of urea acts as a humectant, however at a higher concentration (20-30%) it disrupts the hydrogen bonds or epidermal proteins causing mild keratolysis.

An emollient fills the spaces between skin flakes with droplets of oil which smoothes the skin. Heavy application of the emollient causes it to act like an occlusive. Combination of an emulsifier results in a structure that enables water and oil to be held within the stratum corneum. Vitamin E, mineral oil, fatty acids, cholesterol and structural lipids are examples of emollients. Long chain fatty acids stearic, linoleic, linolenic, oleic and lauric found in palm oil and coconut oil change the properties of the intercellular lipids or the stratum corneum. Ceramide a major component of inner cellular lipids, plays a major role in generating mutilamellae architecture. These are expensive chemicals but they have been shown to be effective in the prevention and improvement of dry skin.

Table 6.1 shows the main ingredients present in an occlusive moisturiser composed of petrolatum and isopropyl myristate. They are hydrophobic and possess the ability to block the TEWL from the skin. The role of aloe barbadensis commonly known as aloe vera, is used to treat skin conditions for example cuts, burns and eczema. It is a superior humectant that has the ability to attract moisture. Terpenoid structures are present within the formulation to provide the aroma of citrus fruits.

Oil phase	**Active agent**	**Terpene**
Petrolatum	Aloe barbadensis	Citral Citronellol
Isopropyl myristate	----------	Limonene Linalool

Table 6.1 Main ingredients of an occlusive moisturiser Vaseline with Aloe Vera

Widely available moisturisers that can be applied daily are usually based on O/W emulsions which do not leave grease on the skin. Table 6.2 shows a typical example of a combination moisturiser which provides humectants (e.g. glycerin), occlusives (e.g. silicones) and emollients (e.g. fatty acids) to the skin. The important NMF found naturally in skin, sodium PCA, is present in the formulation. This will enter the corneocytes, once the lotion has been absorbed by the skin. The tocopherol acetate is used to repair the lipid layer which holds the corneocytes together. This specific type of moisturiser is preferred and there are wide arrays of lotions that target different types of skin providing essential actives, ensuring that adequately hydrated supple skin is maintained. Conventional moisturisers allow the technology used by the cosmetic industry to be fully comprehended allowing the science to be harnessed. A moisturiser is

essentially a vehicle for active agents. The vehicle can be altered in accordance with the actives selected for release.

Water phase	Oil phase	Emulsifier	Actives	Preservatives
Aqua (water)	Caprylic/ Capric Triglyceride	Stearic acid	Tocopheryl acetate (AO)	Methylparaben
Glycerin	Dimethicone	Glyceryl stearate	Sodium PCA (NMF)	Propylparaben

Table 6.2 Main ingredients of a combination O/W moisturiser Dove hydrocare body lotion

An extensive range of moisturisers are available with some possessing excessive price tags. The most expensive cream in the United Kingdom is Crème de La Mer which was launched by Estee Lauder and costs £115 for a pot. It was marketed as an alternative to cosmetic surgery and contained a high quality of actives that are found naturally. However, the precise contents are not disclosed to prevent their technology from being replicated in other moisturisers.

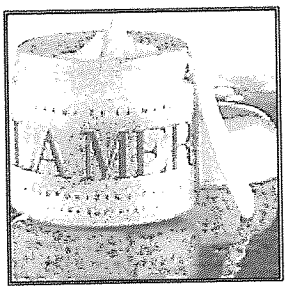


Figure 6.3 Crème de La Mer moisturising face cream

Actives incorporated into creams are of importance especially those found naturally occurring in the skin. The costs of the moisturisers were calculated based upon the vehicle and developmental stages.

6.3 Active agents and their roles

Vast arrays of active agents are widely available and they have various roles within the stratum corneum. A few are highlighted in table 5.3 below.

Active	Log K_{ow}	Function
D-Calcium Pantothenate	-5.35	Water soluble vitamin that promotes wound healing, stimulates epithelisation and has an anti inflammatory effect
Lactobionic acid	-4.89	Water soluble antioxidant also known as a poly hydroxyl acid and normalises stratum corneum exfoliation and thickness. Compatible with sensitive skin and is hygroscopic thereby increasing hydration
PCA	-0.72	Primary NMF found naturally in the stratum corneum, specifically within the corneocytes
Vitamin C	-1.88	Water soluble antioxidant that protects the skin from free radicals which can cause premature ageing
Vitamin E	12.18	Lipid soluble antioxidant and has the potential to repair the lipid barrier within the stratum corneum
Jojoba oil	Unknown	Mimics the action of sebum, which is skins natural lubricant. It cleanses blocked pores, moisturises and promotes a healthy complexion

Table 6.3 Active agents with the corresponding Log K_{ow} value and function

The actives shown have varying solubilities, which range from those of high hydrophilicity (a negative Log K_{ow} value) to no hydrophilicity (a positive Log K_{ow} value).

Log K_{ow} is defined as the Octanol-Water partition coefficient calculated as the ratio of the concentration of the solute in octanol and water at equilibrium using equation 6.1.

$$\text{Log } K_{ow} = \frac{[\text{Solute}]_{\text{octanol}}}{[\text{Solute}]_{\text{water}}} \quad (6.1)$$

In essence the hydrophilicity and hydrophobicity of a chemical can be determined allowing the correct vehicle to be selected which aids the topical delivery of the active.

6.4 Aims

Extensive synthetic work was conducted to design skin adhesive hydrogels which adhere to the skin, for the application of topical delivery. The objective was to utilise monophasic and biphasic gel technologies for the delivery of active agents, which increase the moisture content of skin.

A wide range of active agents are available commercially. A few actives will be selected to show the ease of incorporation and to determine the concentrations that can be accommodated.

It is essential that the incorporation of these actives do not dramatically decrease the adhesivity or alter the mechanical properties of the gel. Structural integrity must be maintained if the gels are to be used as devices to deliver topically.

6.5 Procedure

6.5.1 Incorporation of actives in monophasic compositions

Monophasic gels contain a hydrophilic phase. Therefore, water soluble actives can be incorporated for example d-calcium pantothenate or lactobionic acid. Actives were added to the pregel mixture allowing them to be dissolved with ease, except for PCA. If 1 or 2 % w/w of PCA was added to a monophasic pregel it dissolved. The addition of 3 or 4 % w/w of PCA took up to a day to dissolve and this was dependent upon the pregel composition. If added to a gel composed of AMO, the active dissolved with ease, reducing the time taken to form a homogeneous solution. The addition of PCA to a NaAMPS – AMO based pregel resulted in higher percentages of the active taking more time to dissolve whilst mixing at 150 revs/min. Figure 6.4 shows the theoretical distribution of a hydrophilic active agent within the three dimensional hydrophilic matrix. This configuration can only be achieved if the correct vehicle and corresponding active agents are selected, otherwise phase separation will occur.

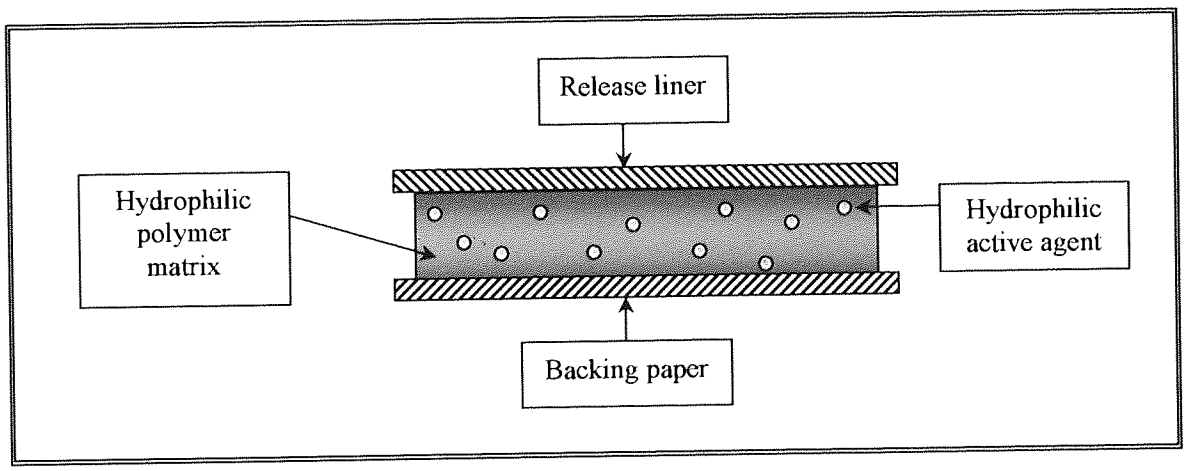


Figure 6.4 Theoretical distribution of a hydrophilic active agent within a three dimensional hydrophilic polymer matrix

6.5.2 Incorporation of actives in biphasic compositions containing hydrophobic monomers

Active agents cannot be added to this type of pregel at the stage before it is polymerised. Ideally, once the pregel forms a homogenous solution, it should not be mixed vigorously. Actives dissolved at this stage may interfere with the stability of the mixture. As shown in previous sections, biphasic pregel components are kept in separate vials during this stage, one contained the hydrophilic chemicals and the other hydrophobic chemicals. The hydrophilic actives were dissolved within the vial containing the hydrophilic components, allowing it to be mixed thoroughly. This ensured that a homogenous solution was obtained. The hydrophobic actives were added to the hydrophobic monomer. This ensured that it completely dissolved within the corresponding monomer. It was encapsulated at this stage and this reduced the probability of phase separation. The theoretical distribution of a hydrophobic active agent within a hydrophilic matrix is highlighted in figure 6.5. The water soluble actives were distributed throughout the hydrophilic polymer matrix as shown in figure 6.4. This type of gel allows the incorporation of both hydrophilic and hydrophobic actives.

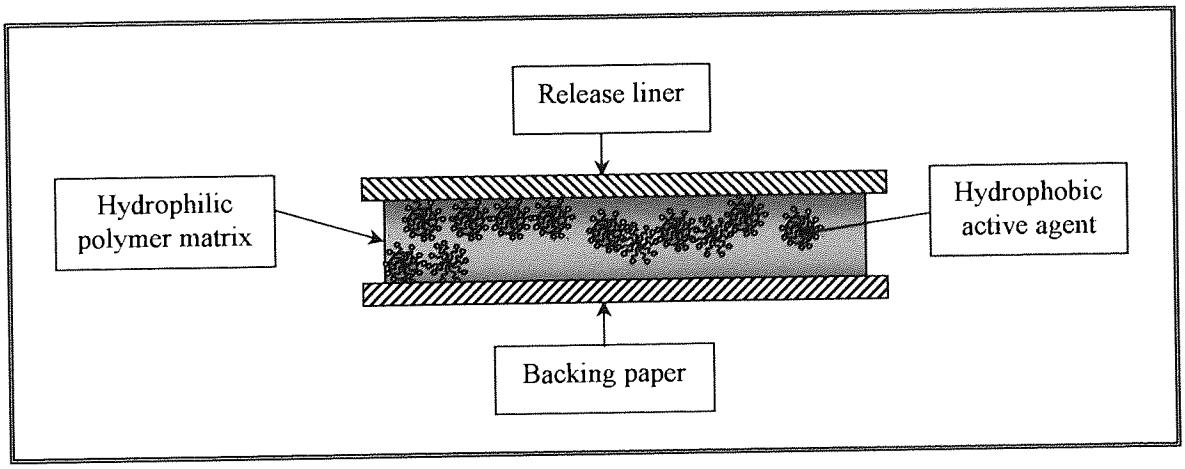


Figure 6.5 Theoretical distribution of a hydrophobic active agent within a hydrophilic polymer matrix

6.5.3 Incorporation of actives in biphasic compositions containing preformed O/W emulsions

A similar procedure to incorporate actives was followed as that used in section 6.5.2. The hydrophilic components were kept in a separate vial from the O/W emulsion. The hydrophilic actives were added to the hydrophilic components of the pregel. The O/W emulsion was handled with due care to ensure that at no stage during the encapsulation process, was it destabilised; by heat or excessive mixing. The hydrophobic active was added to the O/W emulsion and mixed at 50 revs/min for 24 hours. This allowed the hydrophobic active ample time to enter the hydrophobic core of the latex particle, which was visibly detected by the presence of a homogeneous solution. The amount of hydrophobic material added was dependent upon the quantity and the ability of the O/W emulsion to allow more hydrophobic material into its latex core. Figure 6.6 shows the theoretical distribution of a hydrophobic active dissolved within the core of the latex particle of an O/W emulsion in a three dimensional hydrophilic matrix.

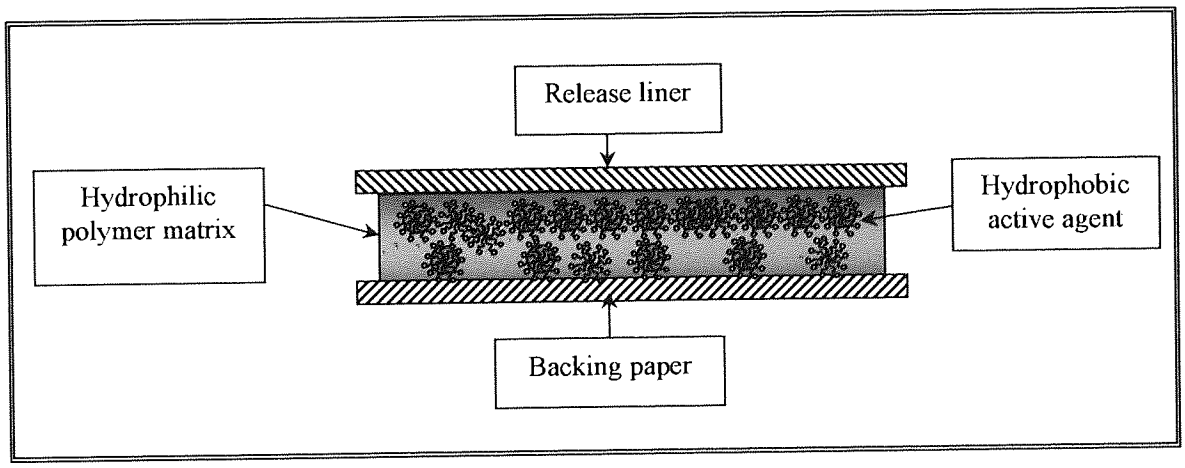


Figure 6.6 Theoretical distribution of a hydrophobic active agent dissolved in an o/w emulsion within a hydrophilic polymer matrix

6.6 Results

6.6.1 Incorporation of D-Calcium Panthothenate to a monophasic hydrogel composition

D-Calcium pantothenate was added to the compositions listed in table 6.4. All of the resultant gels were clear and transparent. Peel strengths of these gels were investigated to ensure that the active incorporated was compatible with the gel composition and that the cohesive or adhesive properties had not been dramatically lowered. The gel containing 0% active possessed a slightly higher peel strength than the gels containing 1 or 2 % w/w of the active. Gels containing 3 or 4 % w/w of the active had higher peel strengths than the monophasic gel containing no actives. The active was therefore adding to cohesive and adhesive strength of the gel through hydrogen bonding, if an adequate amount was incorporated.

NaAMPS (% w/w)	**AMO (% w/w)**	**G (% w/w)**	**H_20 (% w/w)**	**D –Calcium Pantothenate (% w/w)**
21.0	30.0	34.0	15.0	0.0
21.0	30.0	34.0	15.0	1.0
21.0	30.0	34.0	15.0	2.0
21.0	30.0	34.0	15.0	3.0
21.0	30.0	34.0	15.0	4.0

Table 6.4 Compositions of monophasic gels containing D- Calcium Pantothenate

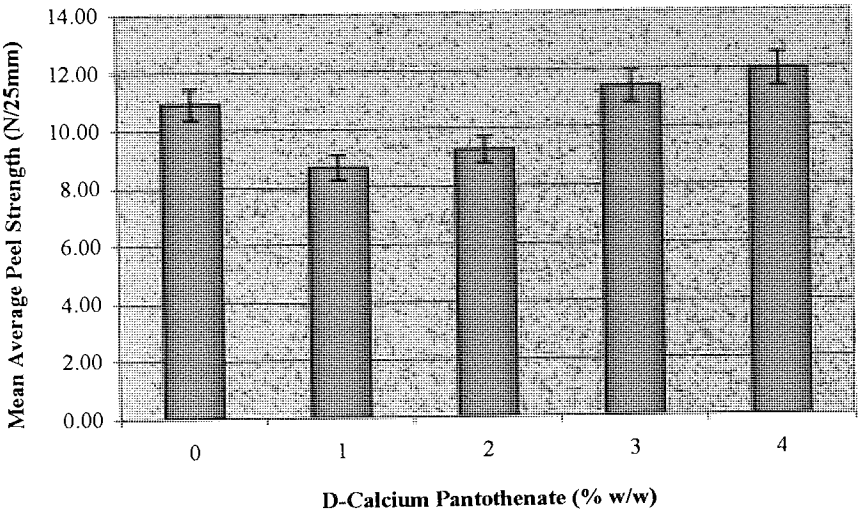


Figure 6.7 Peel strengths of monophasic compositions containing varying amounts of d-calcium pantothenate

Rheological studies on the gels containing 1 or 2 % w/w of the active showed that they had similar elastic and viscous moduli to the gel containing no actives. The gels containing 3 or 4 % w/w had higher elastic and viscous moduli. At low shear the results showed that the gels could be applied with ease to skin and the viscous moduli were within the range stipulated in section 2.3.2.1. At high shear the gel was required to have a dominant elastic component. This would ensure that the gel could be removed in one piece and that no residuals remain on the skin. Figure 6.9 shows that the elastic component was dominant. The gels were removed in one piece. The tan δ value for all of the gels was below 1.0. This highlighted that the elastic component was dominant, a perquisite for a viscoelastic polymer. At higher concentrations the active agent had the ability to interact with the glycerol and water. This reduced the restriction placed upon the polymers and allowed more movement of the polymer chains, which in turn resulted in high elastic and viscous moduli.

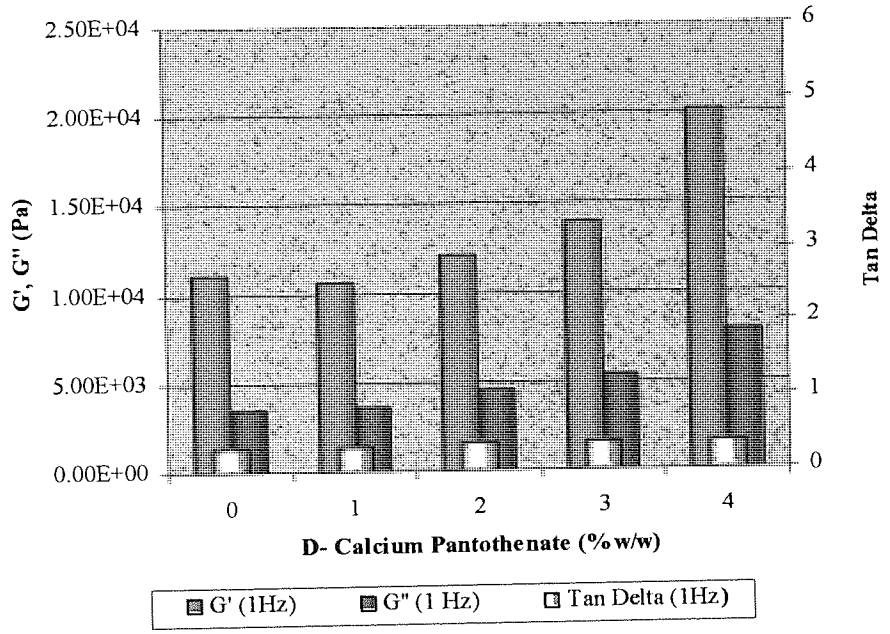


Figure 6.8 Rheological behaviour of monophasic compositions containing varying amounts of D-Calcium Pantothenate at 1 Hz

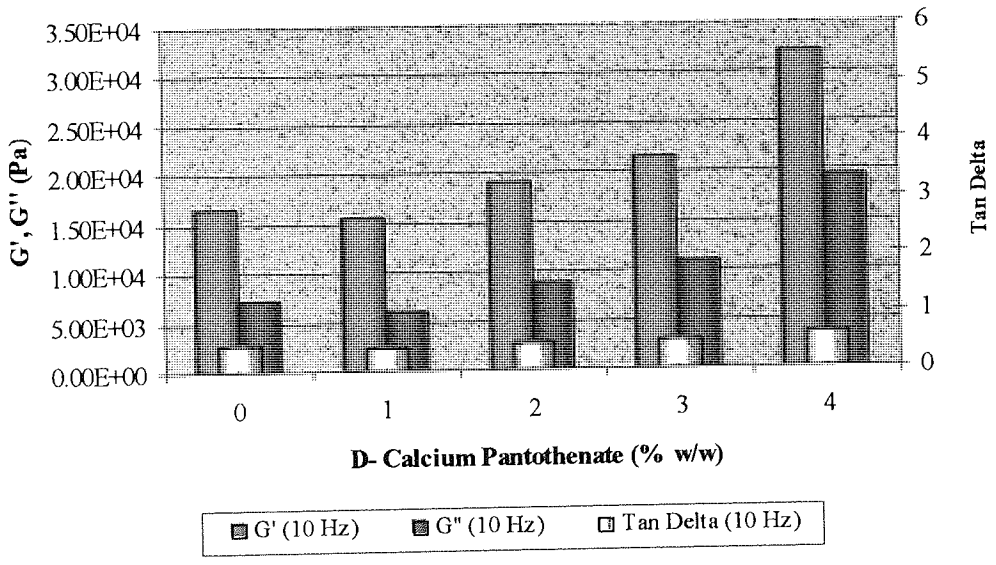


Figure 6.9 Rheological behaviour of monophasic compositions containing varying amounts of D-Calcium Pantothenate at 10 Hz

The active agent was subjected to different levels of moisture to determine its suitability as an active agent using the DVS technique as shown in section 2.3.2.4. The trace shows that a moisture rich environment increases the mass of the active. This indicates that it has a role similar to a humectant and hydrogen bonds with the water. At a relative humidity (RH) of 30% it absorbs more moisture until it reaches approximately 60%. The rate of sorption is higher than the rate of desorption showing that this active is suitable and aids the reduction of dry skin by absorbing moisture.

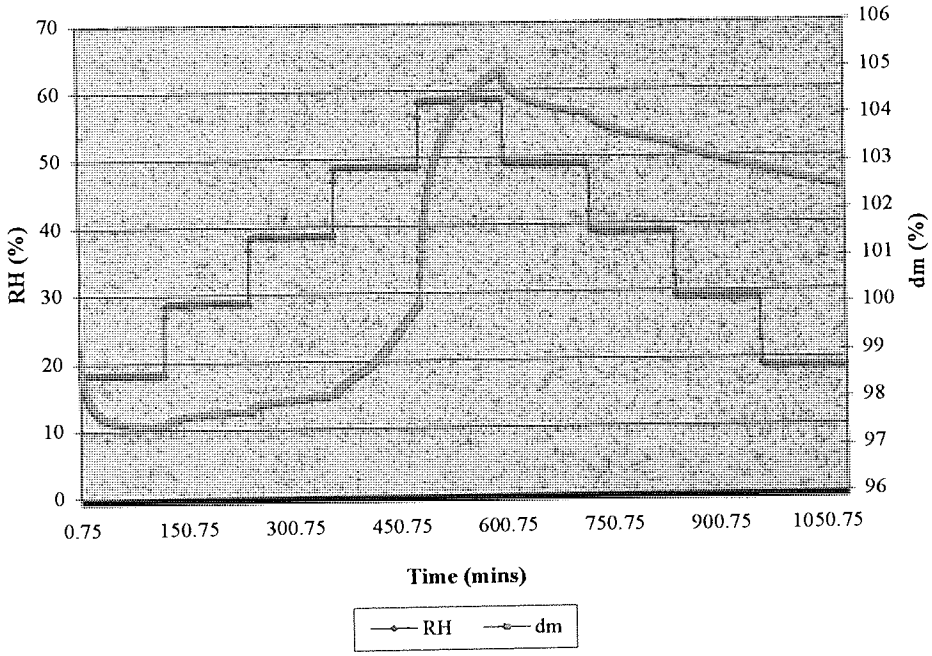


Figure 6.10 DVS trace of D-Calcium Pantothenate

6.6.2 Addition of Lactobionic acid to a monophasic hydrogel composition

Lactobionic acid, a water soluble antioxidant, was added to the compositions as shown in table 6.5. The gels produced were transparent. They possessed good adhesive and cohesive properties. Peel strengths indicated that the addition of the active agent did not interfere with the adhesive and cohesive properties. The presence of the LBA enhanced these properties. The gel containing no active agent had a lower peel strength compared to the gels containing the active agent. The lactobionic acid removed the residual water from the gel, enhancing the cohesive properties which increased the adhesive strength. The addition of 1 % w/w lactobionic acid resulted in the peel strength approximately doubling. This active agent allowed gels of desired peel strengths to be prepared. Incorporation of 1 to 2 % w/w of the lactobionic resulted in the increase of the peel strength.

NaAMPS (% w/w)	**AMO (% w/w)**	**G (% w/w)**	**H_20 (% w/w)**	**Lactobionic acid (% w/w)**
21.0	30.0	34.0	15.0	0.0
21.0	30.0	34.0	15.0	1.0
21.0	30.0	34.0	15.0	2.0
21.0	30.0	34.0	15.0	3.0
21.0	30.0	34.0	15.0	4.0

Table 6.5 Monophasic hydrogels containing the active agent Lactobionic acid

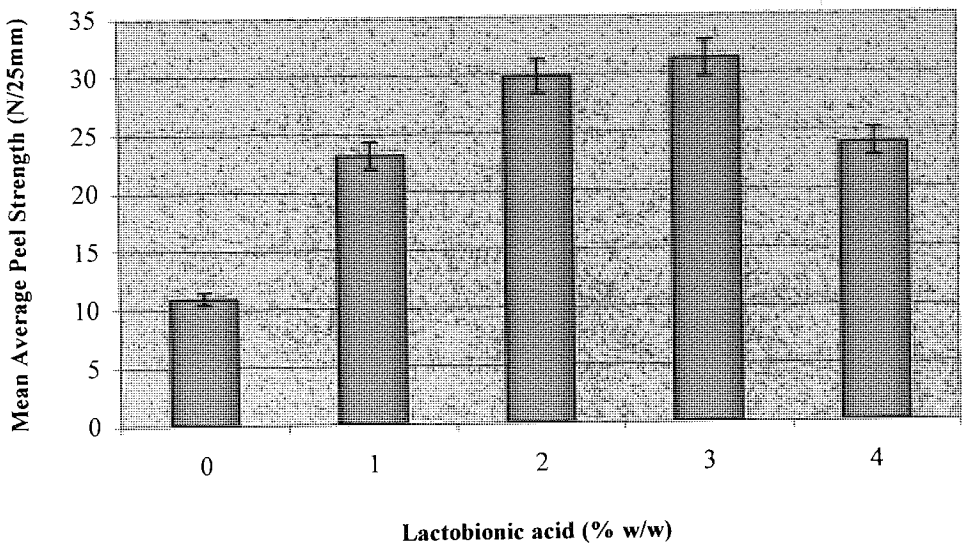


Figure 6.11 Peel strengths of monophasic gels containing varying amounts of Lactobionic acid

Rheological studies showed that the incorporation of actives did not have a detrimental effect on the elastic and viscous moduli of the gels. At low shear rates the elastic modulus was more dominant than the viscous modulus for all of the gels. This indicated that the gels were suitable viscoelastic polymers. The viscous modulus at the low shear showed that the gels were within the range. This highlighted that they could be attached with ease to skin. At high shear rates the elastic modulus showed the ease with which a gel could be removed from the skin. All of the compositions possessed similar values and were within the range stated in section 2.3.2.1.

The compatibility of the active within the hydrophilic matrix allowed large quantities to be added without interfering with its structural integrity. Tan δ values were below 1 at low and high shear stresses. These gels could be used as skin adhesives, since their elastic modulus was greater than the viscous modulus for those composed.

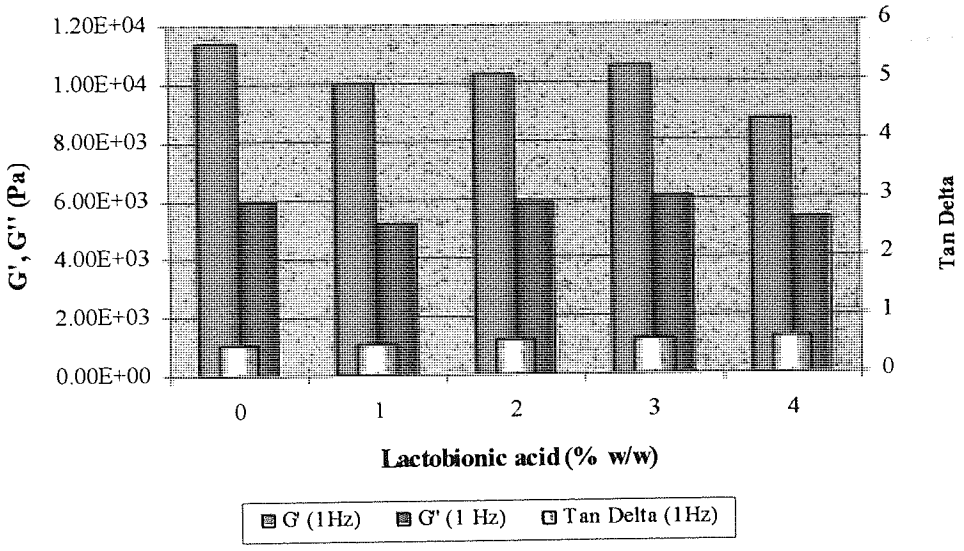


Figure 6.12 Rheological behaviour of monophasic gels containing varying amounts of Lactobionic acid at 1 Hz

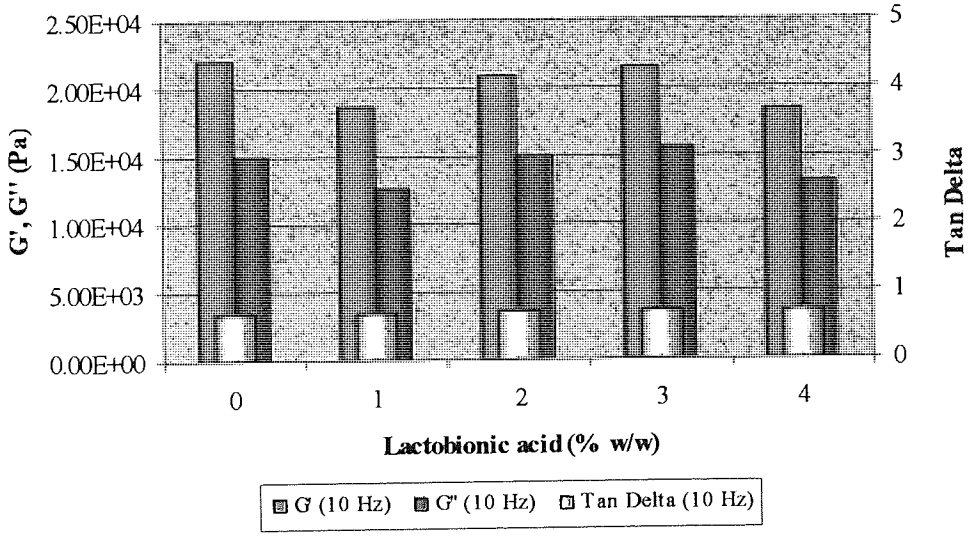


Figure 6.13 Rheological behaviour of monophasic gels containing varying amounts of Lactobionic acid at 10 Hz

The DVS trace showed that lactobionic acid had the potential to absorb and hold moisture. Moisture is lost via desorption at slower rates. At a relative humidity of 40 %, the solid

active begins to absorb moisture which halts at 60 % RH according to the test parameters inputted before the experiment was carried out. The rate at which moisture desorbs from lactobionic acid is faster than the desorption rate of d-calcium pantothenate which was expected. The latter active agent is more hydrophilic than the previous and will therefore take a longer period of time for it to lose all of its moisture.

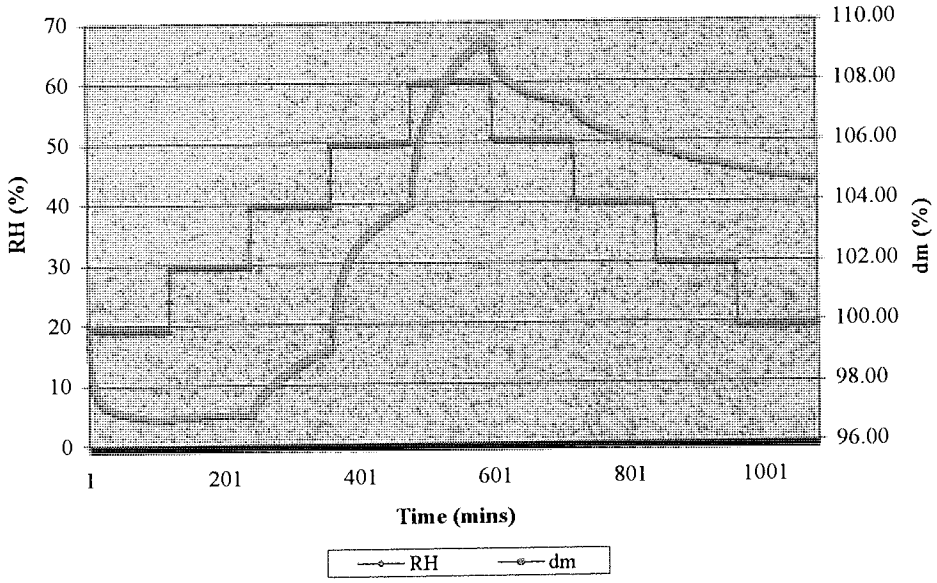


Figure 6.14 DVS trace of lactobionic acid

Figure 6.15 displays the DVS trace obtained for a NaAMPS – AMO gel. It showed the relative rates of sorption and desorption at different RH values. This highlighted that storage in a moisture free environment is essential. The absorption of water is known to interfere with the adhesion of the gel. Figure 6.16 and 6.17 show the DVS traces of the gels containing 1 or 2 % w/w of LBA respectively. The addition of these actives did not dramatically alter the absorption or desorption of the gels.

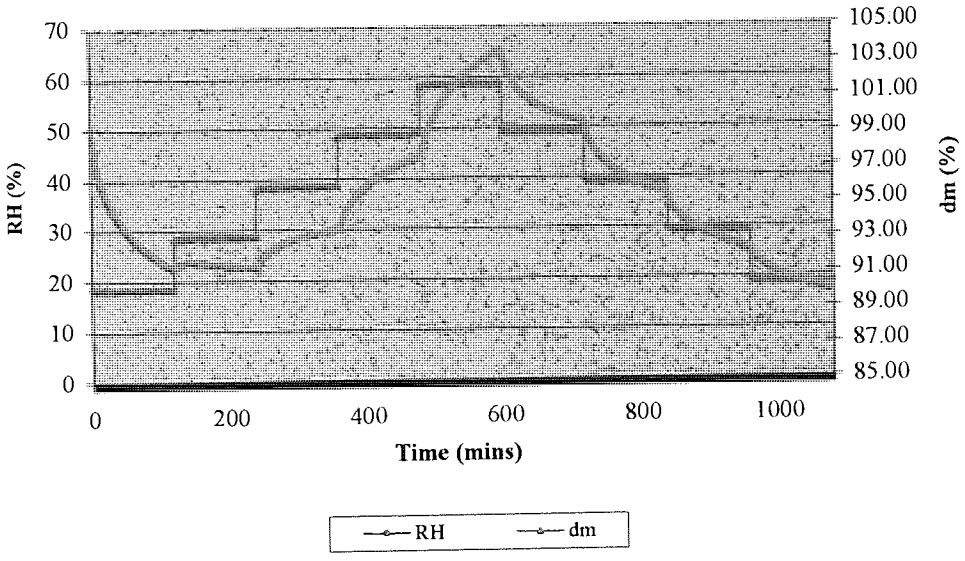


Figure 6.15 DVS trace of monophasic NaAMPS- AMO gel

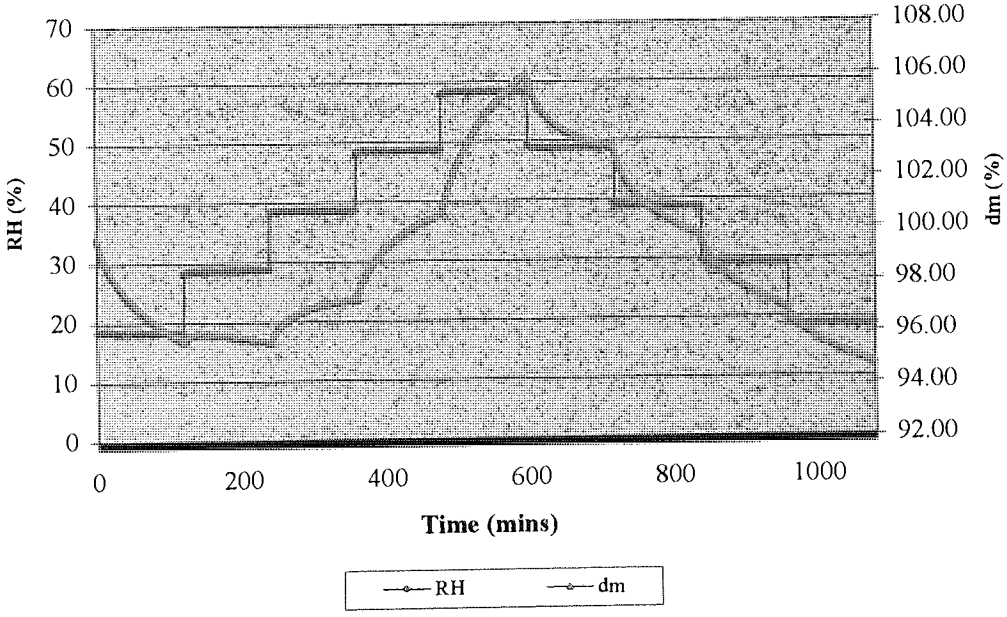


Figure 6.16 DVS trace of 1% lactobionic acid in a monophasic gel

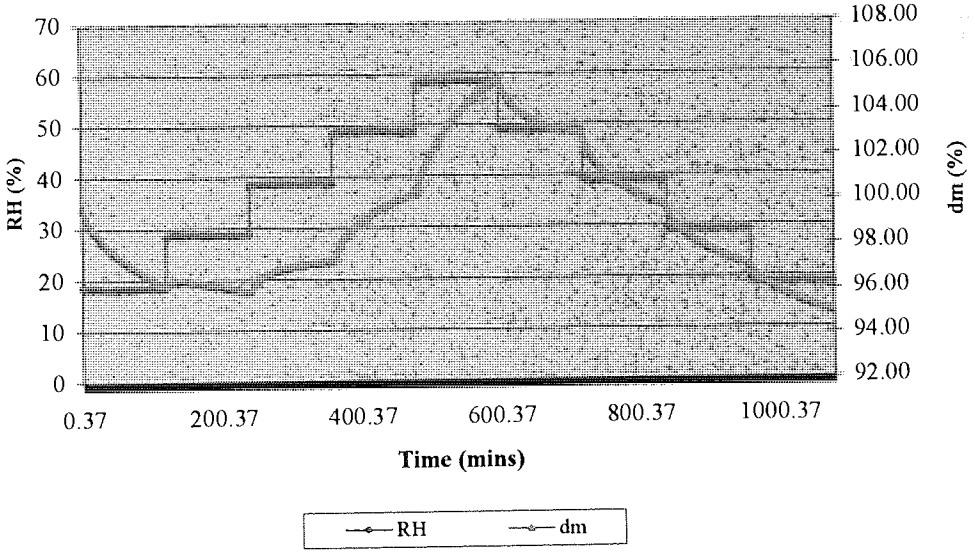


Figure 6.17 DVS trace of a monophasic gel containing 2% LBA

6.6.3 Addition of PCA to a monophasic gel composition

PCA, the primary NMF was incorporated into the monophasic gel formulations listed in table 6.6. PCA was not as soluble as LBA or d-calcium pantothenate, and therefore the addition of 1 or 2 % w/w resulted in gels that possessed good adhesive and cohesive properties. The addition of 3 or 4 % w/w of PCA reduced the cohesivity of the gels. The hydrophobic content of the gel increased on the addition of PCA, and ultimately resulted in the reduction of the cohesive and adhesive properties.

The DVS trace of solid PCA (figure 6.18) shows the moisture absorption capacity of this natural moisturising factor. As the humidity increased, moisture was absorbed. The humidity was reduced and the PCA did not lose any of the moisture. It held on tightly to it showing that it is an excellent moisturiser. It did not release moisture as was shown by LBA and d-calcium pantothenate.

NaAMPS (% w/w)	AMO (% w/w)	G (% w/w)	H_20 (% w/w)	PCA (% w/w)
21.0	30.0	34.0	15.0	1.0
21.0	30.0	34.0	15.0	2.0
21.0	30.0	34.0	15.0	3.0
21.0	30.0	34.0	15.0	4.0

Table 6.6 Composition of monophasic gels containing 1.0, 2.0, 3.0 or 4.0 % w/w of PCA a natural moisturising agent

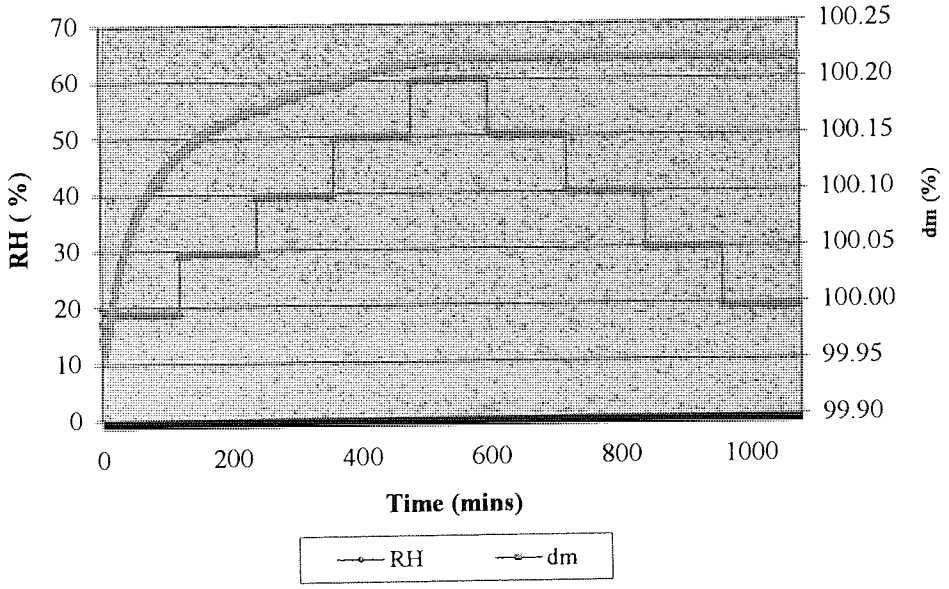


Figure 6.18 DVS trace of solid PCA

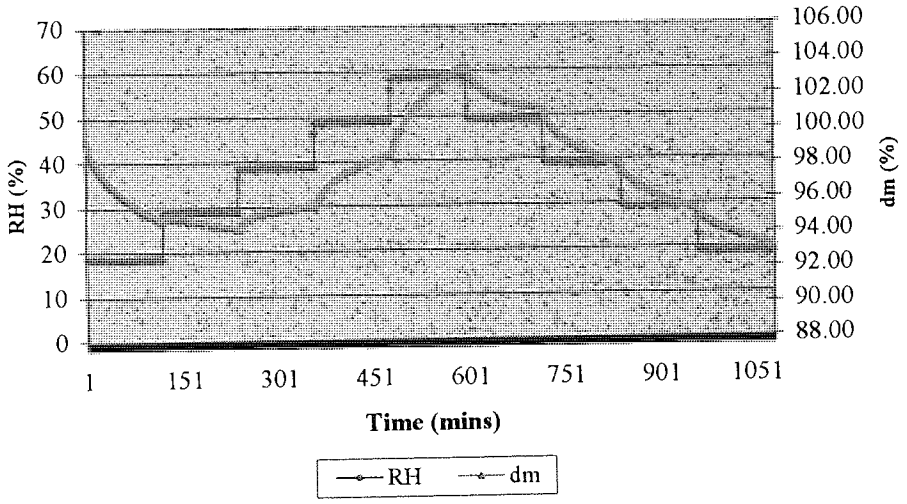


Figure 6.19 DVS trace of 1 % PCA in a monophasic gel

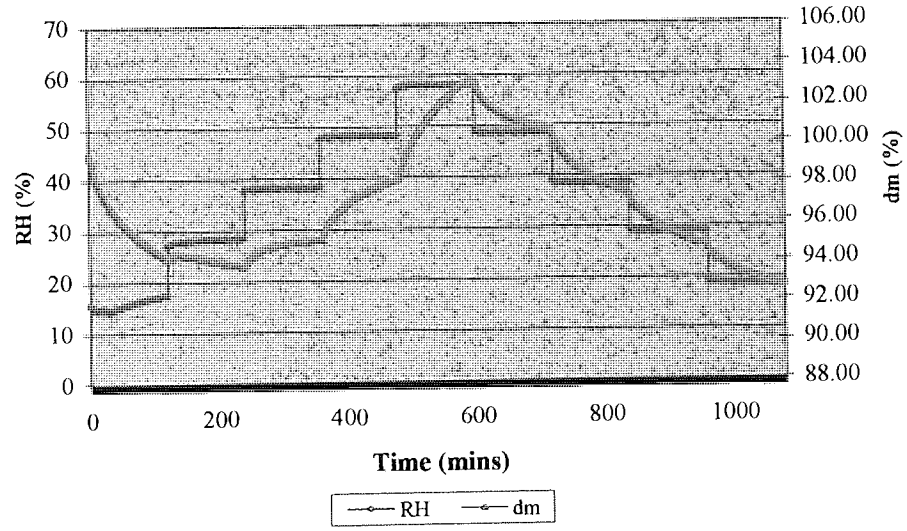


Figure 6.20 DVS trace of 2 % PCA in a monophasic gel

6.6.4 Incorporation of PCA & Vitamin E to biphasic skin adhesive hydrogels

6.6.4.1 Gel compositions containing the hydrophobic monomer ESBA

Biphasic hydrogels have the capacity to hold active agents with different solubilities. The mechanical properties of the biphasic gels with compositions as shown in table 6.7 were measured. The rheological studies showed that gels containing no actives and with actives gave similar results. At low and high shear rates the elastic modulus was greater than the viscous modulus for all of the gels. These were the properties expected from the viscoelastic polymers. The incorporation of PCA reduced the viscous flow of the gel. Vitamin E decreased the viscous flow to a greater extent than the PCA. The incorporation of both actives to the gel resulted in the viscous component increasing. The gels possessed elastic and viscous moduli which allowed them to be placed onto the skin and removed in one piece with ease.

NaAMPS (% w/w)	AMO (% w/w)	ESBA (% w/w)	Tn 60 (% w/w)	PCA (% w/w)	Vit E (% w/w)
29.0	19.0	3.0	0.9	0.0	0.0
29.0	19.0	3.0	0.9	1.0	0.0
29.0	19.0	3.0	0.9	0.0	1.0
29.0	19.0	3.0	0.9	1.0	1.0

Table 6.7 Biphasic hydrogels containing the hydrophobic monomer ESBA and different actives

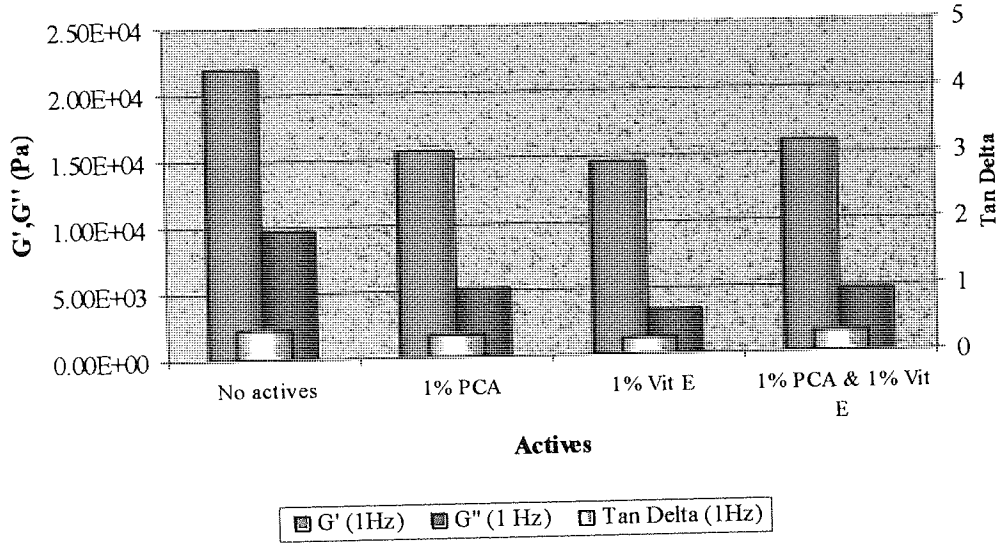


Figure 6.21 Rheological behaviour of biphasic hydrogels containing ESBA and active agents 1 Hz

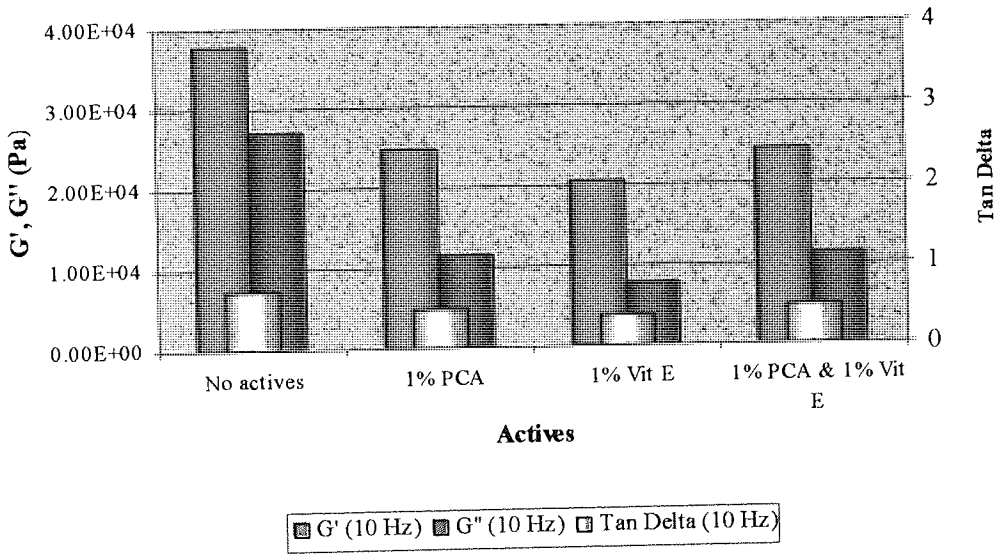


Figure 6.22 Rheological behaviour of biphasic hydrogels containing ESBA and active agents 10 Hz

6.6.4.2 Gel compositions containing the hydrophobic monomer LA

Gels with compositions shown in table 6.8 were made up and subjected to mechanical testing in order to determine their rheological properties. At low and high shear rate the elastic modulus was dominant over the viscous modulus, showing that the gels were viscoelastic. Values were lower than those previously measured for the ESBA containing gels. This can be accounted for by the incorporation of a smaller hydrophobic monomer which is more mobile. The results show that at low shear with the incorporation of PCA, Vitamin E or a combination of both, the mechanical properties were not altered dramatically.

The elastic modulus at low shear showed that the ease with which the gel could be attached to the skin was similar for the various compositions. At high shear rate the elastic component gave an indication of the gel being removed in one piece. The results showed that its removal left no residue behind, so structural integrity was maintained. The gels show similar trends and have similar properties when compared to monophasic gels.

NaAMPS (% w/w)	**AMO (% w/w)**	**LA (% w/w)**	**Tn 60 (% w/w)**	**PCA (% w/w)**	**Vit E (% w/w)**
29.0	19.0	3.0	0.9	0.0	0.0
29.0	19.0	3.0	0.9	1.0	0.0
29.0	19.0	3.0	0.9	0.0	1.0
29.0	19.0	3.0	0.9	1.0	1.0

Table 6.8 Biphasic hydrogels containing the hydrophobic monomer LA and different actives

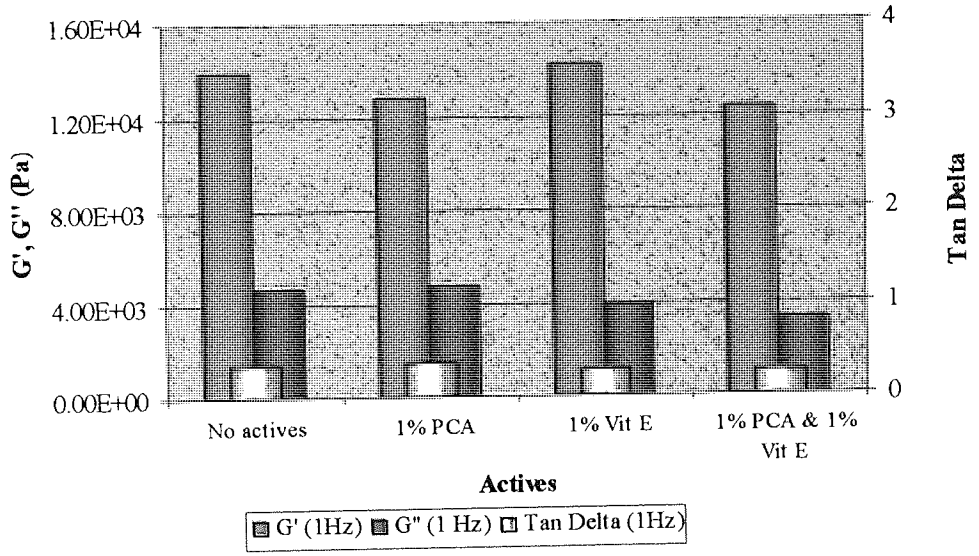


Figure 6.23 Rheological behaviour of biphasic hydrogels containing LA and active agents 1 Hz

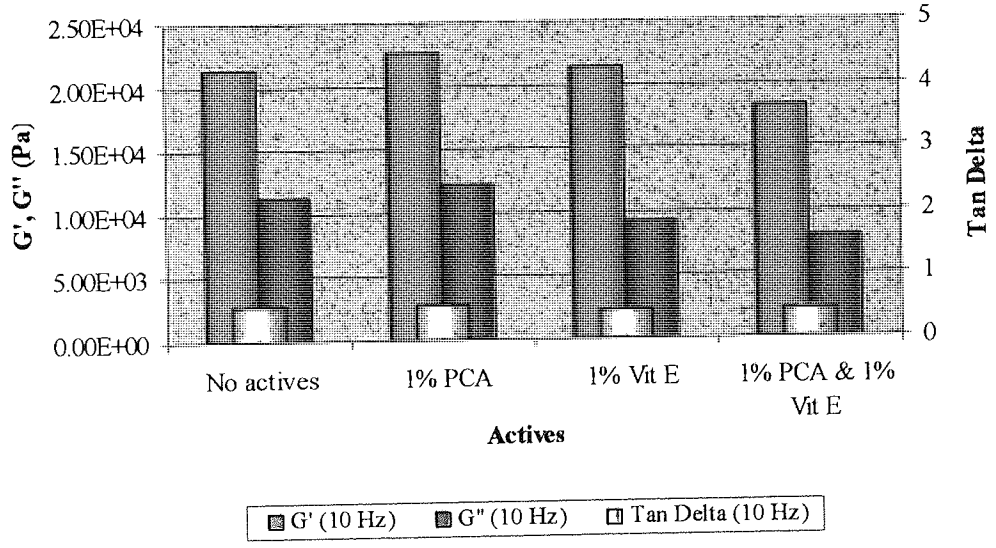


Figure 6.24 Rheological behaviour of biphasic hydrogels containing LA and active agents 10 Hz

6.6.4.3 Gel compositions containing the hydrophobic monomer SA

Biphasic hydrogels containing SA, a hydrophobic monomer, were synthesised using the formulations listed in table 6.9. The gels containing combinations of actives, PCA and Vitamin E, possessed a higher elastic and viscous modulus than the corresponding gels with no actives. Comparing the rheological data with those of LA, the elastic and viscous moduli observed were less than those for the latter. The results were within the ranges stipulated in section 2.3.2.1 and showed that these gels have acceptable viscoelastic properties. At low shear rate the viscous modulus showed the ease with which gels can be attached to the skin. The results indicated that the gel containing both the PCA and Vitamin E could be attached to the skin with a greater degree of ease, when compared to the other compositions. At high shear stress the elastic modulus was important as this showed the ease with which the gel could be removed in one piece without leaving a residue. All of the gels were removed with ease and the data showed that the gel containing both actives was the most elastic gel.

NaAMPS (% w/w)	AMO (% w/w)	SA (% w/w)	Tn 60 (% w/w)	PCA (% w/w)	Vit E (% w/w)
29.0	19.0	3.0	0.9	0.0	0.0
29.0	19.0	3.0	0.9	1.0	0.0
29.0	19.0	3.0	0.9	0.0	1.0
29.0	19.0	3.0	0.9	1.0	1.0

Table 6.9 Biphasic hydrogels containing the hydrophobic monomer SA and different actives

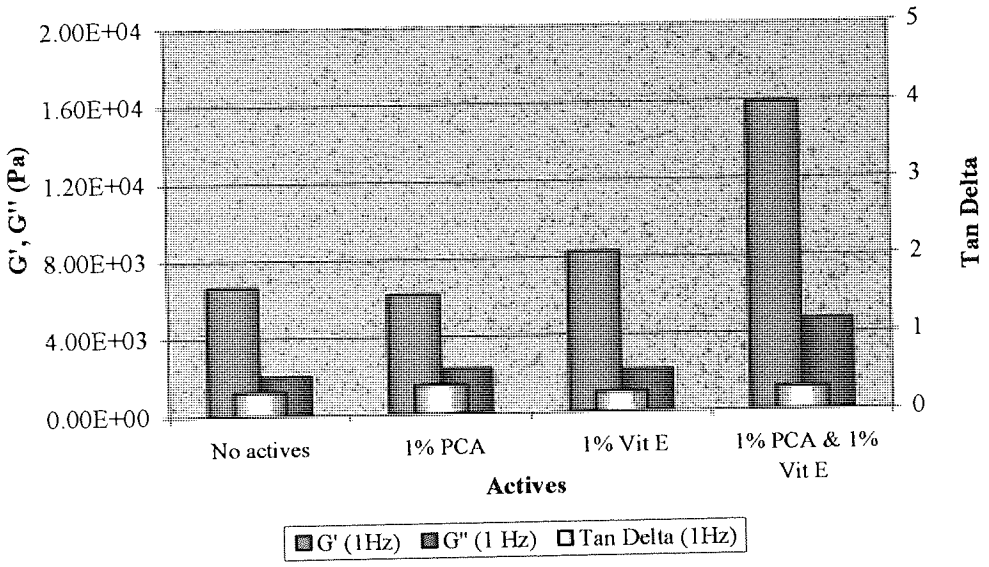


Figure 6.25 Rheological behaviour of biphasic hydrogels containing SA and active agents 1 Hz

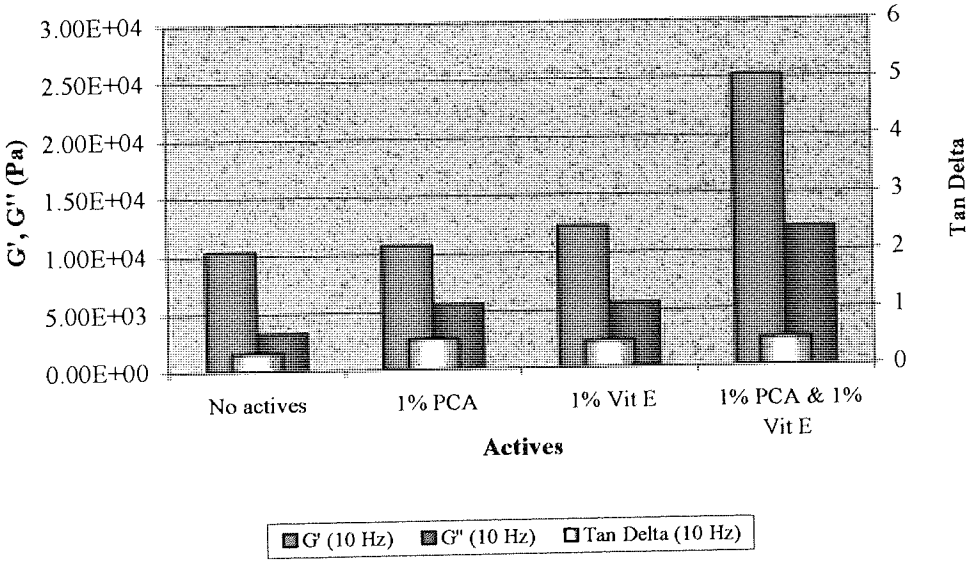


Figure 6.26 Rheological behaviour of biphasic hydrogels containing SA and active agents 10 Hz

6.6.5 Incorporation of Jojoba oil to biphasic skin adhesive hydrogels containing a preformed commercial O/W emulsion

Biphasic gels were made up using the formulations shown in table 6.10. The quantities of glycerol and water added to each gel were 26.4 and 13.3 % w/w respectively. Addition of the jojoba oil to the pregel solution resulted in phase separation. Therefore, the oil was added to Texicryl 13056WB. The solution was mixed on an IKA VIBREX shaker set at 50 revs/min for twenty four hours. The oil was encapsulated within the emulsion and no traces of it were visible in the aqueous phase.

The gels formed were opaque and possessed good cohesive strength. The objective of this section was to show the potential application of commercial O/W emulsion as a carrier for hydrophobic actives. Incorporation of lipophilic actives could result in destabilisation of the emulsion. Therefore, slow mixing was required to allow its diffusion into the hydrophobic core or the excess surfactant micelles within the emulsion.

NaAMPS (% w/w)	**AMO (% w/w)**	**Texicyl 13056WB (% w/w)**	**Tn 60 (% w/w)**	**Jojoba oil (% w/w)**
18.3	12.4	28.6	1.0	1.0
18.3	12.4	28.6	1.0	2.0
18.3	12.4	28.6	1.0	3.0
18.3	12.4	28.6	1.0	4.0

Table 6.10 Biphasic hydrogels containing Texicryl 13056WB and Jojoba oil

6.6.6 Incorporation of PCA to biphasic skin adhesive hydrogels containing a preformed commercial O/W emulsion

Compatibility of the emulsion and PCA was investigated in this section. Gels were made up as indicated in table 6.11. The quantities of glycerol and water added to each gel were 26.4 and 13.3 % w/w respectively. The addition of PCA to monophasic gels showed that if more than 2% w/w was added the structural integrity was impaired. However, addition to the O/W emulsion showed that it was soluble above this value. PCA was highly compatible with the biphasic gels and did not destabilise the emulsion during the preparation of the gels.

NaAMPS (% w/w)	**AMO (% w/w)**	**Texicyl 13056WB (% w/w)**	**Tn 60 (% w/w)**	**PCA (% w/w)**
18.3	12.4	28.6	1.0	1.0
18.3	12.4	28.6	1.0	2.0
18.3	12.4	28.6	1.0	3.0
18.3	12.4	28.6	1.0	4.0

Table 6.11 Biphasic hydrogels containing Texicryl 13056WB and PCA

6.7 Discussion

The solubility of an active can be used to determine the appropriate gel technology that should be selected to accommodate it. In the previous chapters, it was established that the incorporation of extra components into a pregel mixture, could result in a decrease in the adhesive and cohesive strength of the photopolymerised gel. D-Calcium pantothenate, a hydrophilic active agent, was added at 1, 2, 3 and 4 % w/w to monophasic pregel solutions. Corresponding skin adhesives possessed peel strengths similar to those of the gel containing no active. The gels containing 0 – 3 % w/w of d- calcium pantothenate had similar elastic and viscous moduli at low and high shear rate showing that the incorporation of this active agent did not have a negative effect on the structural integrity. The gel containing 4% w/w of d-calcium pantothenate possessed a high viscous and elastic component. This was accounted for by an increase in hydrogen bonding, which increased the cohesiveness of the gel. Molecular motions were restricted, therefore the gel could not flow as effectively as a gel containing a lower percentage of this active.

1-4 % w/w of lactobionic acid, a water soluble active, was incorporated into monophasic pregels and yielded gels with high peel strengths of over 20 N/25mm. The active was an excellent adhesion promoter and produced higher peel strengths than the gels containing acrylic acid. The advantage of incorporating this active was that it allowed the adhesion to be controlled, whilst providing a moisturiser to the skin to maintain the appropriate level of hydration. This active did not alter the viscous or elastic properties of the gel and allowed the structural integrity to be maintained.

The incorporation of PCA into a monophasic pregel was only viable if 1 or 2 % w/w was added since over 2 % w/w of PCA interferred with the structural integrity of the gel. An increase in the quantity of PCA added increased the hydrophobicity of the pregel, which compromised its integrity. PCA could be incorporated into biphasic technology gels with ease. The hydrophobic monomer, within the pregel, provided an area where the hydrophobic portion (-CH_2 groups on the pyrrole ring) of PCA can interact leaving the

hydrophilic portions (>C=O, >COOH and –NH groups) free to interact with the predominantly hydrophilic components.

DVS traces of d-calcium pantothenate, lactobionic acid and 2-pyrrolidone-5-carboxylic acid showed the relative affinity of these actives to absorb or desorb water when placed into a moisture rich or deficient environment. Samples were placed into the DVS instrument, which was interfaced to a computer to collate the results. They showed that d-calcium pantothenate and lactobionic acid were good humectants. They absorbed moisture when the humidity was increased and that desorption took place at a slower rate. PCA is known as the primary NMF and has the capability of absorbing moisture as the humidity is increased. When the humidity was decreased it did not lose moisture showing how essential it is to have this active agent within the skin and its water binding property.

Biphasic gels containing ESBA, LA or SA allowed the incorporation of both hydrophilic and hydrophobic active agents, without resulting in reduced rheological properties of the gel. Gels containing LA showed similar properties to monophasic gels. Taking into consideration the phase separation pattern displayed in the previous chapter, this gel would be ideal for topical delivery. Commercial O/W preformed emulsions allowed the incorporation of an array of actives. The hydrophobic actives were located within the latex particle and hydrophilic actives were within the aqueous phase.

Chapter 7

In vitro & in vivo release studies

7.1 Introduction

7.1.1 In vitro release

This thesis focuses upon the topical delivery of actives to the stratum corneum to maintain the optimum levels of moisture. Appropriate active agents were incorporated in skin adhesive hydrogels. The release was monitored to ensure that the actives were not bound within the polymer matrix and to determine whether the quantity released would have a significant effect. The method used to measure the in vitro release required the selection of suitable skin substitutes. In 1979, the first reconstructed epidermis topped with a horny layer was developed for grafting major burns, which formed a valuable model for testing new pharmaceutical and cosmetic products. Taking into consideration that this type of skin substitute is very costly was being studied another alternative was selected.

As stated in chapter 5, the stratum corneum is composed of an aqueous phase consisting of specialised corneocytes which contain water soluble NMFs, which are bound together by lipids. In order to monitor the release of an array of active agents, a simple system was designed using polymeric mimics of the aqueous and lipoidal phases. Poly HEMA was used as the aqueous analogue. Water was contained within its polymer matrix and silastic, a silicone rubber, was selected as the lipoidal analogue due to its hydrophobic nature. The aqueous or lipoidal phase mimic measuring 2cm x 2cm were placed on a clean glass plate as shown in figure 7.1. It was covered with the skin adhesive hydrogel loaded with a NMF measuring 1.5cm x 1.5cm. The glass plate was covered with "cling film" to ensure that the environment was kept isolated to allow the continuity of experimental conditions. Release was terminated by the removal of the skin adhesive hydrogel from the aqueous or lipoidal mimic. The NMF or hydrophobic actives were extracted respectively into water or a lipoidal solution and analysed using UV spectroscopy, which allowed the concentrations of the actives released from the polymer matrix to be determined.

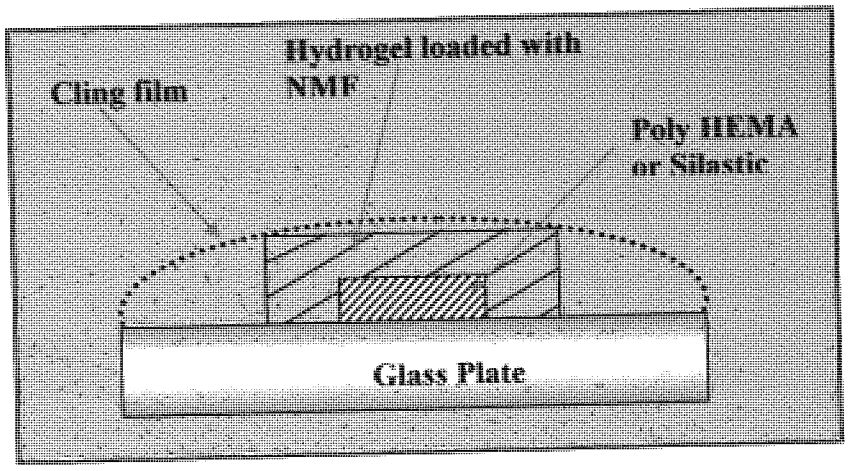


Figure 7.1 NMF release apparatus

7.1.2 In vivo release

In vitro release provided essential information about the capability of the three dimensional polymer matrix to release the active agents into either an aqueous or lipoidal mimic. In vivo studies are more restrictive due to ethical and financial issues. This thesis addresses topical delivery, therefore in vivo release of actives to the stratum corneum should be investigated. The effects of NMFs in skin could be monitored using non invasive and invasive methods. Gels were placed onto the author's arm as shown in figure 7.2. The skin was not pretreated with any form of external moisturiser prior to testing. This area was selected since a lower amount of sebum is produced on this part of the body. This natural oil would interfere with the release tests giving inaccurate results and it would hinder the release of hydrophilic active agents into the skin. This area is easily accessible and allows numerous release studies to be conducted in tandem.

Tests were repeated on the forearms after three weeks. This gave the skin enough time for cell renewal. This process is slow and must not be disturbed as it will result in a weaker SC barrier being formed which may result in the initiation of the desquamation process, whilst the skin strives to reach its optimum standard of protection.

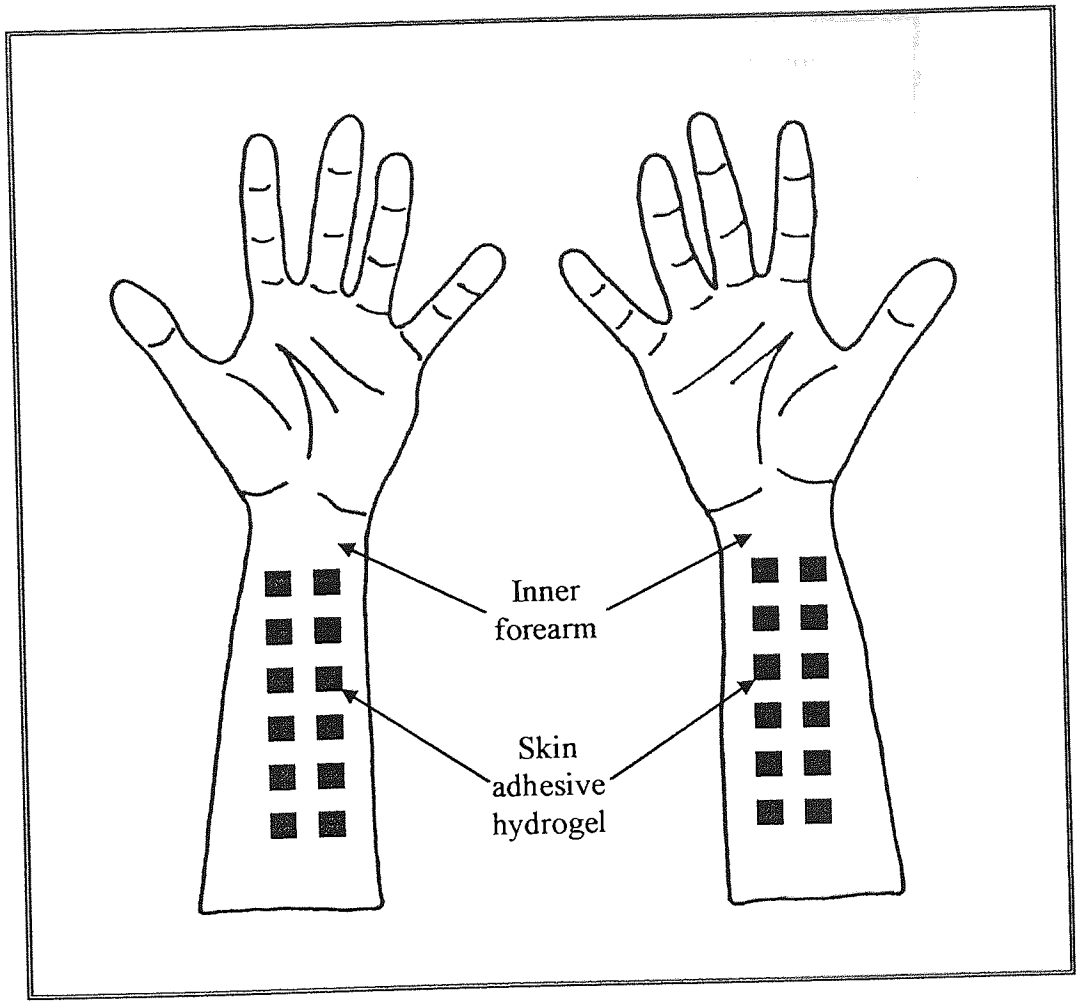


Figure 7.2 In vivo release tests conducted on the forearms

A simple non invasive method for skin analysis involves a machine known as the skin reader MY- 610. It uses bioelectric impedance analysis (BIA) technology to immediately and automatically detect the factors that effect the skin condition, for example moisture, oil and softness. The probe head contains two electrodes which are applied to the skin. Upon contact, it provides a low intensity electrical current which allows the electrical resistance to be measured. The presence of water in skin affects its conductivity proportionally. A larger quantity of water results in greater conductivity and therefore lower resistance. The data is displayed on the LCD on the front of the skin reader and can be correlated with the index of measurements shown in tables 7.1 – 7.3 to understand the condition of the skin.

Moisture

Indicator range	Skin condition
-1 to +1	Ordinary skin
Over - 3	Partially dry
Over + 3	Partially humid

Table 7.1 Skin reader MY- 610 moisture indicator range and skin condition

Oil

Indicator range	Skin condition
-3 to +3	Ordinary skin
Over - 3	Partially dry
Over + 3	Partially oily

Table 7.2 Skin reader MY- 610 Oil indicator range and skin condition

Softness

Indicator range	Skin condition
-1 to +1	Ordinary skin
Over - 2	Partially rough
Over + 2	Partially soft

Table 7.3 Skin reader MY- 610 softness indicator range and skin condition

The level of skin hydration can be measured with the aid of a Corneometer CM 825. The measurements are based upon the physical principle of a common capacitor. Typically it consists of two metal plates that are electrically insulated by a medium, which acts as a dielectric for example either air, glass, plastic or vacuum. Application of a uniform charge field to the capacitor causes an excess build up of electrons on one plate (negative charge) and a lack of electrons on the other plate (positive charge). When the source is removed the plates retain their charge. A capacitor has the capability of storing electrical charge. When the capacitor is put into contact with molecules it results in their polarization, one end will have a negative charge and the other a positive charge. The charges on the plates are partially compensated by an opposite charge, which results in the capacitor storing more charge and increasing its capacity. The capability of a dielectric to increase the capacity of a capacitor is dependant upon the material.

Water increases the capacity of the capacitor when compared to a vacuum by a factor of approximately eighty one times. When relating this fact to another material for example skin, it shows that by altering the degree of water within the skin causes a large change in the capacitance. The probe used to take measurements is electrically isolated from the measurement electronics which eliminate various factors that could influence the measuring system, for example earth capacity has no influence. External influences for example temperature or air humidity can have an effect on the humidity of skin which will in turn affect the actual measurement displayed by the corneometer. It is essential to keep the test conditions consist allowing the results to be compared. Skin hydration is different for all individuals. It varies for males and females and with age. The measuring process of the corneometer involves the application of a probe to skin, which is activated when it is pressed down. The measured values were recorded within a computer linked to the device using the CKA-MPA-Multi-Probe-Adapter version 1.4.1.8 software package. The data obtained can be correlated with the results displayed in table 7.4, to determine the condition of the skin. All values displayed had arbitrary units.

Indicator range	Skin condition
< 30	Very dry
30 - 45	Dry
> 45	Sufficiently moisturised

Table 7.4 Corneometer CM 825 values and skin condition

The moisture levels of the stratum corneum can be measured by tape stripping this layer from skin and analysing with Fourier Transform Attenuated Total Reflectance (FT – ATR) spectroscopy. 3M Magic Scotch tape was a good tape which removed layers of the stratum corneum. They were analysed and the tape did not interfere with the results obtained. In the early 1960s Fahrenfort and Harrick developed the ATR technique which used an optical element of high refractive index. When light passed from a material with a high refractive index to one with a lower refractive index it is normally totally reflected.

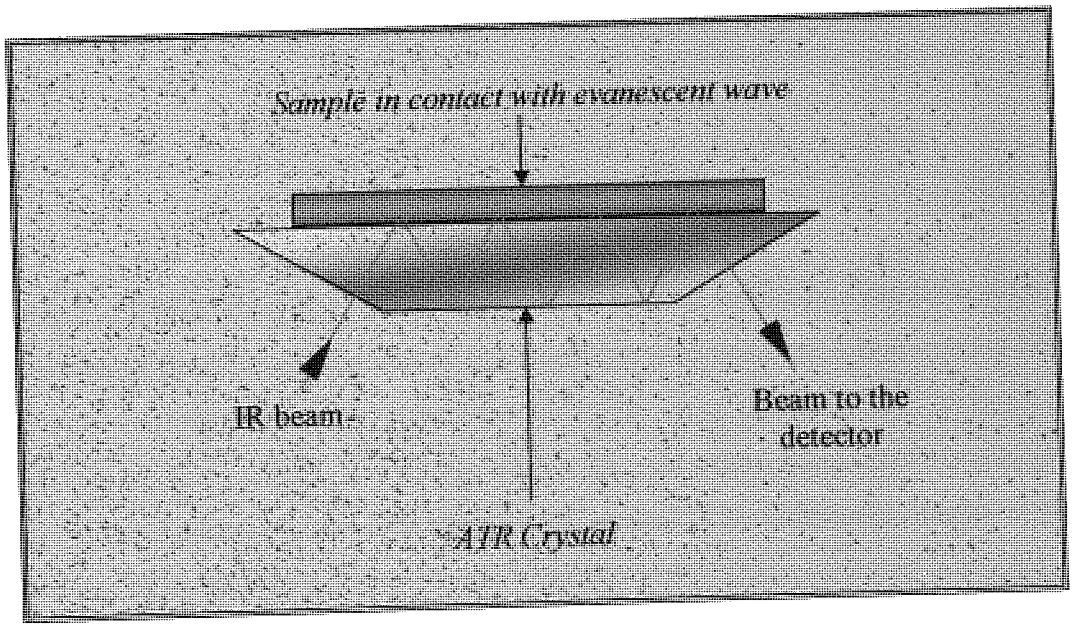


Figure 7.3 A typical attenuated total reflectance system

In practice the light can partially enter the material with a lower RI and be absorbed resulting in attenuated reflected beam. An ATR accessory is essential in enabling the changes that occur to the totally internally reflected beam to be measured, when it comes into contact with the sample. The total internal reflectance is achieved when the angle of incidence exceeds the 'critical' angle. Equation 7.1 shows that the 'critical' angle θ_c is a function of both the crystal (n_1) and sample (n_2) refractive indices.

$$\theta_c = \sin^{-1} (n_2/n_1) \tag{7.1}$$

As shown in figure 7.2 an IR beam is directed into the optically cense ATR crystal which has a high refractive index at a certain angle. The internal reflectance creates an evanescent wave which extends beyond the surface of the crystal into the sample which is in contact with it. An analogy used to explain the evanescent wave is a bubble of IR that sits on the surface of the crystal and only protrudes a few microns into the sample. This varies with the type of crystal used. The depth of penetration of the evanescent wave (d) is defined as the distance from the crystal-sample interface, where the intensity of the evanescent decays to 1/e (37%) of its original value and can be calculated using equation 7.2. The wavelength of infrared radiation is denoted as λ and θ is defined as the incident radiation.

$$d = \lambda / \{2\pi n_1 [\sin^2 \theta - (n_2/n_1)^2]^{1/2}\} \tag{7.2}$$

The depth of penetration and the total number of internal reflections can be controlled by varying the angle of incidence and or the type of crystal selected. Good contact between the sample and the ATR crystal must be achieved in order to ensure that the beam enters the surface of the sample. In regions of the IR spectrum, where the sample absorbs energy, the evanescent wave is attenuated or altered. The attenuated energy is passed back to the IR beam which then exits the opposite end of the crystal and is passed to the detector to generate an IR spectrum.

7.2 Aims

Skin is hydrated through a natural control mechanism, which maintains an optimum environment. A breakdown in the levels of moisture and lipid result in inadequate moisturisation, which ultimately leads to the dehydration of skin. Long term use of skin adhesive hydrogels will result in the removal of the stratum corneum. NMFs are essential for maintaining the moisture levels within the skin. This chapter investigates the release of various active agents incorporated in skin adhesive hydrogels ensuring that they can increase the hydration of stratum corneum.

Both in vitro and in vivo studies should be investigated, in order to monitor the release of active agents. Skin adhesive hydrogels containing the active agents are required to deliver topically. Therefore, in vitro release should be investigated using a suitable aqueous and lipoidal skin mimic to represent the stratum corneum of the skin. Qualitative analysis should be carried out to highlight that actives can be released from the three dimensional polymer matrix.

A range of techniques used to monitor skin hydration by in vivo studies include both non invasive and invasive methods. Utilisation of the bioelectric impedance analysis, conductance and IR analysis are essential to understand the condition of the skin before and after release. Selected active agents must promote skin hydration and this should be established.

In vitro and in vivo testing should allow the suitability of the technology and the active agents to be determined, ensuring that they can promote the level of hydration without compromising the stratum corneum barrier, which would ultimately lead to its breakdown.

7.3 Procedure

7.3.1 Preparation of Poly HEMA & Silastic

The three dimensional matix of homopolymeric HEMA was prepared in accordance with the redox polymerisation method stated in 2.3.1.2. The silastic was synthesised by mixing 30g Silastic 3481, 3g Silastic 81VF the curing agent and 1g Silastic thixo additive in a large glass jar. The mixture was placed between two melinex sheets. Pressure was applied ensuring that approximately 2mm thick sheets were formed.

7.3.2 Tape stripping & Analysis

3M Magic Scotch tape was used to remove the layers of the skin from the stratum corneum located on the inside of the forearm. Moisturisers or active agents placed onto the skin, were rubbed in and left for approximately one hour. After this time a piece of tape was applied to the skin and pressed down by rolling a 25g weight over it twice. The tape was them removed from the skin which was analysed by FT ATR. A diamond crystal set within the accessory known as the 'Golden Gate' was used and a beam of IR was reflected once.

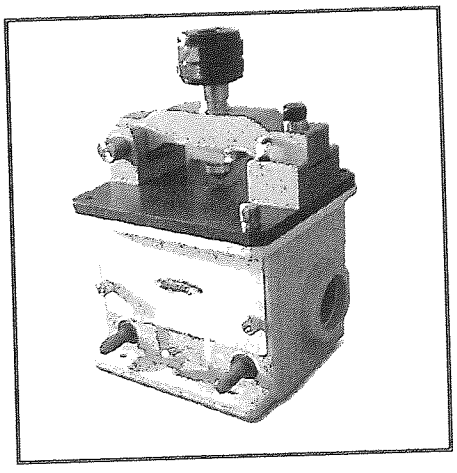


Figure 7.4 The 'Golden Gate' accessory containing a diamond crystal

7.4 Results

7.4.1 In Vitro Release of Hydrophilic Actives from Monophasic Skin Adhesive Hydrogels

Monophasic hydrogels were made up as shown in section 6.5.1 and polymerised using redox initiators Oxone and ascorbic acid. They contained 1, 2, 3 or 4 % w/w of one of the following active agents PCA or LA. The K_{ow} values for PCA and LA are -0.72 and -0.65 respectively, which showed that these NMFs have a greater affinity for water than lipid. The experimental studies confirmed their affinity and are shown in figure 7.5 and 7.6. The aqueous substrate composed of Poly HEMA containing water, was favoured over the lipoidal substrate silastic for both NMFs. Nonetheless there was appreciable penetration into the lipoidal mimic. The stratum corneum structure consists of a lipid bilayer which provides a means of entry for most topically applied active agents. The active agent present in the lipoidal substate highlighted that both PCA and LA possessed the correct solubility parameters and size, allowing their release from skin adhesive hydrogels.

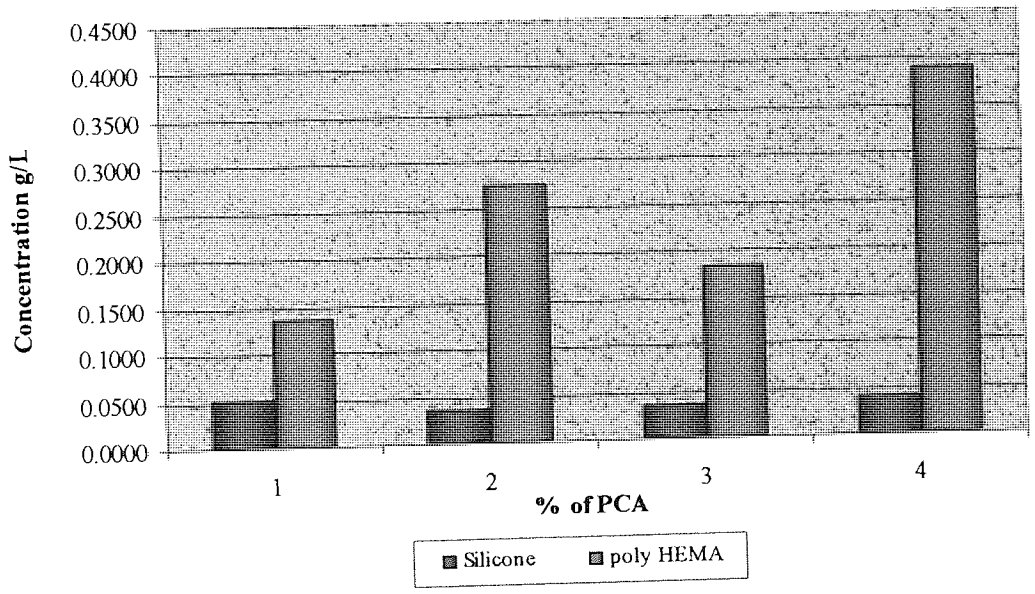


Figure 7.5 PCA release from a monophasic skin adhesive hydrogel into Poly HEMA and Silastic over 24 Hours

PCA is more hydrophilic than LA and results confirmed this by showing elevated levels of PCA release compared to the latter NMF. The results show that PCA the main NMF which is found naturally within the stratum corneum can be delivered topically and is capable of being partitioned between the aqueous and lipoidal routes.

The levels of LA release are lower than that of PCA, despite being loaded into a similar three dimensional polymer matrix. The monophasic gels were composed of the hydrophilic components NaAMPS, AMO, glycerol, water and Irgacure 184 and Ebacryl II as the PI/ XL system. Due to the size, structural affinity, log K_{ow} and charge of the LA interacted with the matrix, reducing the amount that was free to be released. However, the levels at which the LA were released are by no means non beneficial. They are sufficient enough to stimulate the growth of collagen and elastin to improve the quality of the skin. Lactic acid is generally classified as an alpha hydroxy acid with a role as an exfoliant. It causes the cells of the epidermis to become 'unglued' allowing the cells to slough off, promoting the regrowth of new skin. High concentrations of lactic acid increased the rate of sloughing. If it is faster than the rate of cell renewal it will result in problems arising with the skin barrier.

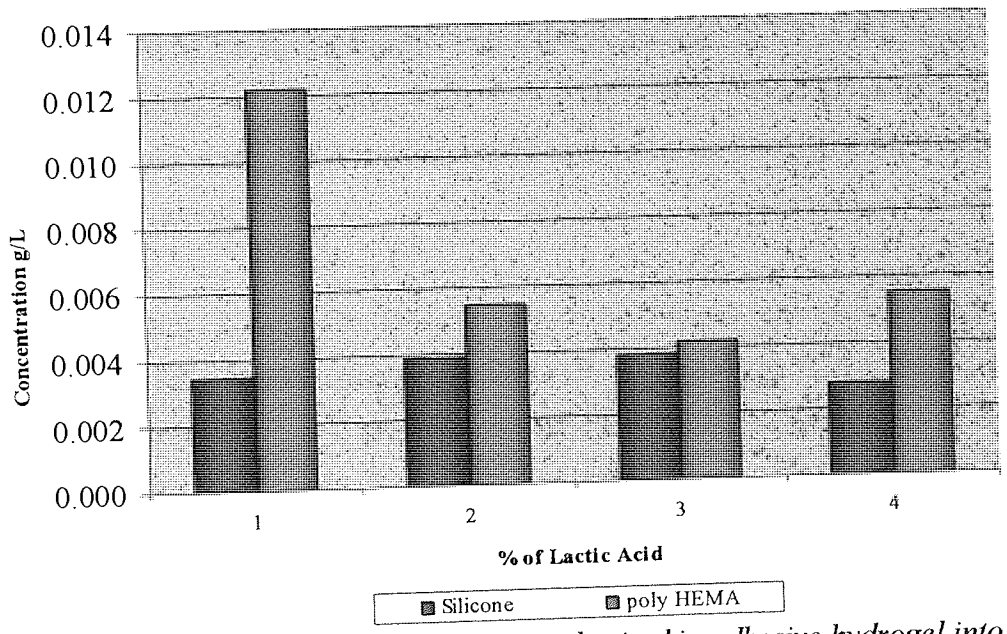


Figure 7.6 Lactic acid release from a monophasic skin adhesive hydrogel into Poly HEMA and Silastic over 24 Hours

7.4.2 Release of Hydrophilic / Hydrophobic Actives Agents from Monophasic and Biphasic Hydrogels

The previous section investigated the release of water soluble NMFs from a three dimensional hydrophilic matrix. There are a number of factors, as discussed in section 1.5.9, that can result in the decrease in the moisturisation of the stratum corneum. Essentially this layer is composed of a hydrophilic component which is contained within the corneocytes and a hydrophobic component which holds the latter together. For a short term solution in particular skin that is slightly dehydrated, with the barrier still intact, it is acceptable to release only water soluble actives. When the water content of the skin is less than 10 %, it results in a reduction of NMF within the stratum corneum. They bind to water within this layer and lower amounts result in tightness of the skin.

A further reduction in the water content results in the breakdown of the lipid layer which holds the corneocytes together. An increase in the rate of trans epidermal water loss (TEWL) is observed. Biphasic technology was utilised to allow an array of active agents with varying solubility or K_{ow} values to be incorporated within the three dimensional polymer matrix. The most essential NMF PCA, was selected as the hydrophilic active and Vitamin E as the hydrophobic component to potentially aid in the repair of the lipid layer. The log K_{ow} suggests that PCA is five times more attracted to the aqueous phase than to the lipid phase, but it is capable of being partitioned between both as illustrated in the previous section.

Figures 7.7 and 7.8 show the concentration of NMF/lipid constituent extracted from the aqueous/lipoidal substrate repectively. The moisturising agent PCA favoured the aqueous substrate whereas Vitamin E preferred the lipid substrate. A limitation is placed upon the solubility of actives that can be added to monophasic gels. Therefore, only hydrophilic actives can be incorporated and released. Biphasic hydrogels can be utilised to deliver both hydrophilic and hydrophobic actives with preferential release of the latter. This study illustrates that it is possible to release NMFs/ hydrophobic actives from a biphasic hydrogel through an aqueous/ lipoidal route respectively with release profiles adjusted to

give the required delivery characteristics. Vitamin E released from biphasic hydrogels into the lipid layer of the skin will counteract the problems that arise. When the moisture needs to be locked within the stratum corneum this type of active is beneficial. It gives skin enough time to continue its natural moisturisation process which produces water in the underlying layers to the stratum corneum. This migrates towards the top layers of the skin but it is a time consuming process. The octanol water partition coefficient of Vitamin E is 12.18 and this value shows that it has a greater affinity for lipids than water. Vitamin E has a dual functionality; it repairs the lipid barrier and plays a role in the reduction of the lipid peroxidation process.

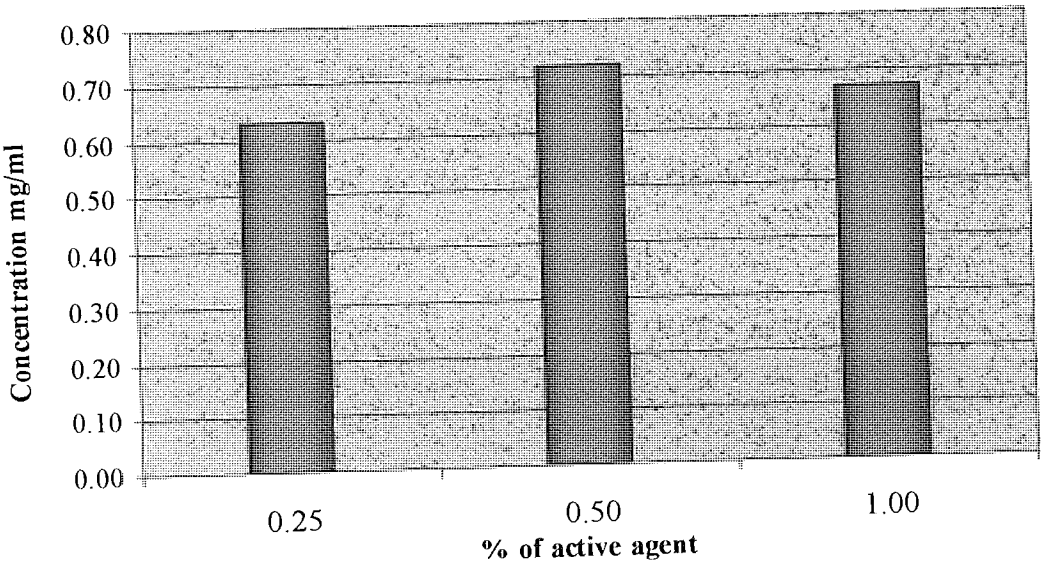


Figure 7.7 A Graph to Show the Concentration of PCA Released From A Monophasic Skin Adhesive Hydrogel Over 24 Hours

The release of PCA from monophasic gels is greater than that from biphasic gels however the quantities released will play a significant role in counterbalancing the moisture content of dry skin. Monophasic gels containing 0.25% or 0.50 % w/w PCA released approximately four times the quantity when compared to biphasic compositions containing the same amount and the monophasic gel containing 1.00 % w/w PCA had double the release rate of its biphasic equivalent. Upon further investigation of the release of Vitamin E from biphasic gels, highlighted that more hydrophobic material was

released when compared to the hydrophilic NMF, PCA. Taking into consideration that Vitamin E is a larger molecule than PCA and more hydrophobic one would expect more PCA to be released. However, this was not the case and can be explained by the location of the hydrophobic polymer within the matrix. Vitamin E is located within the hydrophobic polymer matrix and the PCA within the hydrophilic three dimensional polymer matrix. As shown by optical microscopy in a previous chapter there is a substantial amount of hydrophobic polymer located at the surface of the skin adhesive. This aids the release of the hydrophobic component, Vitamin E, in higher concentrations, whilst allowing the release of the hydrophilic active PCA.

Excessively dry skin with a moisture content below 10 %, would benefit from water soluble NMF and Vitamin E released from a biphasic gel. This technology will provide sufficient amounts of hydrophilic and hydrophobic actives to the skin. Supplying the skin with these components would aid the repair of the barrier whilst allowing underlying layers of skin to repair from within.

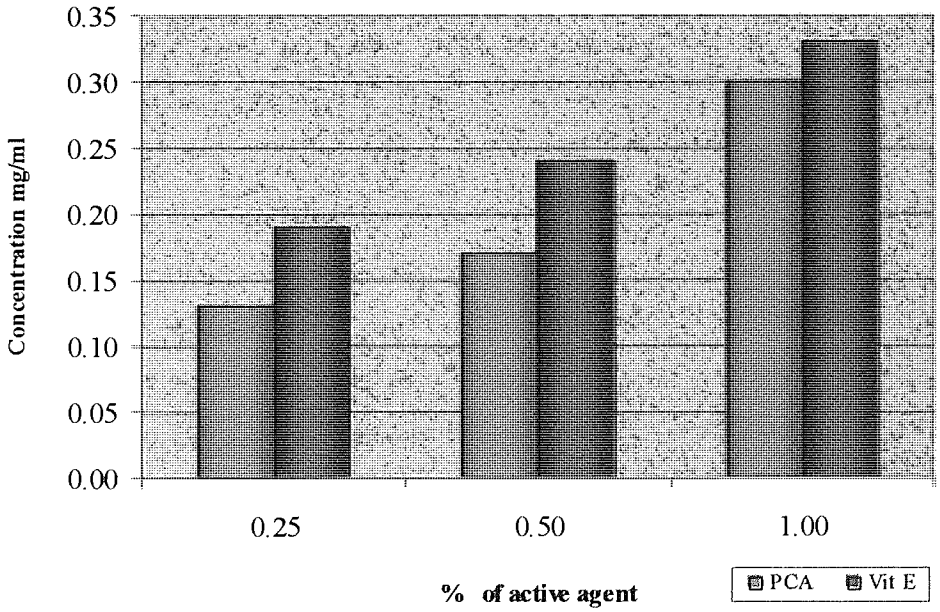


Figure 7.8 A Graph To Show The Concentration of PCA & Vitamin E Released From A Biphasic Skin Adhesive Hydrogel Over 24 Hours

7.4.3 Investigating the effects of release of an antioxidant Lactobionic acid into banana peel

Lactiobionic acid is a polyhydroxy acid (PHA). It is less harsh than lactic acid an alpha hydroxyl acid (AHA), known for its role for modulating keratinisation. This process makes way for cell development within the stratum corneum. When a person ages, this process slows down the exfoliation process. Cells remain on the skin which causes a rough and uneven texture. A distinct advantage of this active agent is that it is compatible with sensitive skin. It has a larger molecular size, when compared to lactic acid and allows gentle application, which decreases the sensitivity and discomfort.

This section looks at the quantitative release of lactobionic acid from monophasic skin adhesive hydrogels, highlighting in particular its antioxidant role. Banana peel was used as an aqueous mimic and showed that under normal conditions one expects it to discolour within a few hours. This is due to the breakdown of its structure, depending on the oxidative conditions. Five different skin adhesive hydrogels samples containing 0, 1, 2, 3 & 4 % w/w of lactobionic acid were prepared in accordance with the method stated in section 6.6.2. Samples measuring 1.5cm x 1.5 cm were cut and placed on to banana peels also cut to 2.0 x 2.0 cm. Release studies were carried out for fifty four hours in total and the results are displayed in figure 7.10.

The gels from left to right contained 0 to 4 % w/w LBA respectively. At thirty two hours the banana peel in contact with the gel containing 0 % w/w of the active agent began to discolour, whereas the other banana peels in contact with the hydrogels containing 1, 2, 3 or 4 % LBA did not discolour. After forty hours they were re-examined and they all showed signs of discolourment. The release of the LBA had diminished considerably and the power of the antioxidant had reduced when compared to previous interactions of the LBA. It prevented the oxidative degradation of the banana peel.

The results showed that the water soluble LBA was delivered during a forty hour time frame and did not require a tailor made hydrogel as required to deliver over types of antioxidants. The majority of these agents are lipophilic (e.g. Vitamin A or Vitamin E). A hydrogel containing 1 % w/w LBA is potent enough to ensure that the degredation of the banana peel is slowed down.

Lactobionic acid has numerous roles including one as an antioxidant which can play a major part in slowing down the visible signs of ageing and it also has the ability to co-ordinate with excess iron in the skin reducing oxidative damage. (Womens Wear Daily, 2003). The most important and relevant role is that it has excellent humectant properties and binds strongly with water. Figure 7.9 shows the interaction of some of the groups on the LBA molecule with water through hydrogen bonding. All of the sites cannot bind with water because it would lead to steric hinderance from adjacent groups.

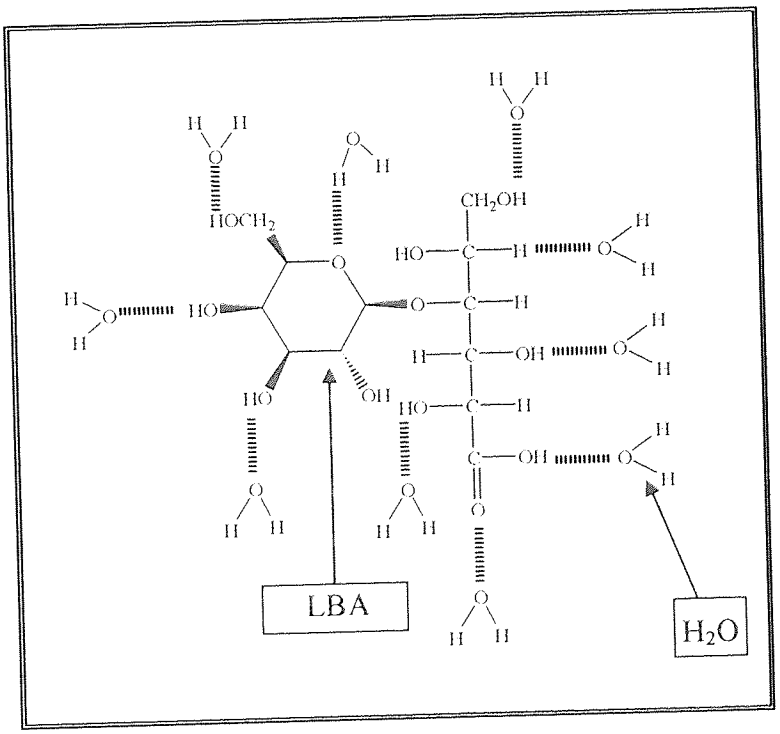


Figure 7.9 Water binding potential of Lactobionic acid

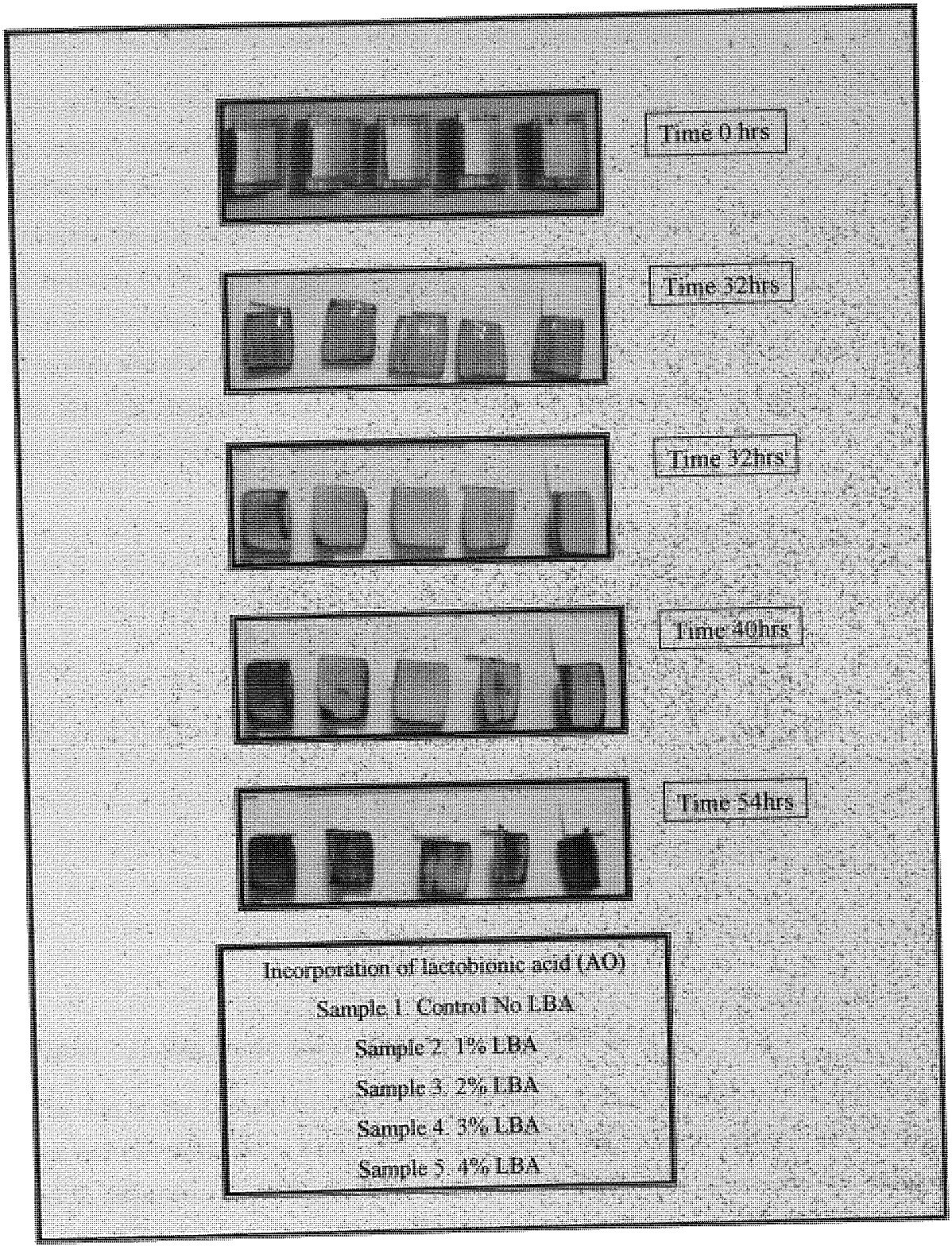


Figure 7.10 Antioxidant potential of lactobionic acid in skin adhesive hydrogels (Sample No 1 to 5 left to right respectively)

7.4.4 In Vivo Release Monitoring Using the Skin Reader MY-610

This technique was used to highlight the importance of using one specific site of the body to conduct release studies. As shown in figure 7.11 the moistness, oiliness, roughness/ softness of the skin varied for the arm, forehead and neck. Tables 7.1 – 7.3 were used to interpret the data displayed. The skin on the author's arm was dry. The low levels of oil contributed to the dryness of the skin. Moist skin is associated with soft supple flexible skin and the results show that the arm was ideal for carrying out moisturisation studies. The neck and chin yielded similar results and upon consultation with the ranges displayed, the skin was classified as ordinary. This highlighted that an adequate level of moisture and oil were present, resulting in smooth supple skin.

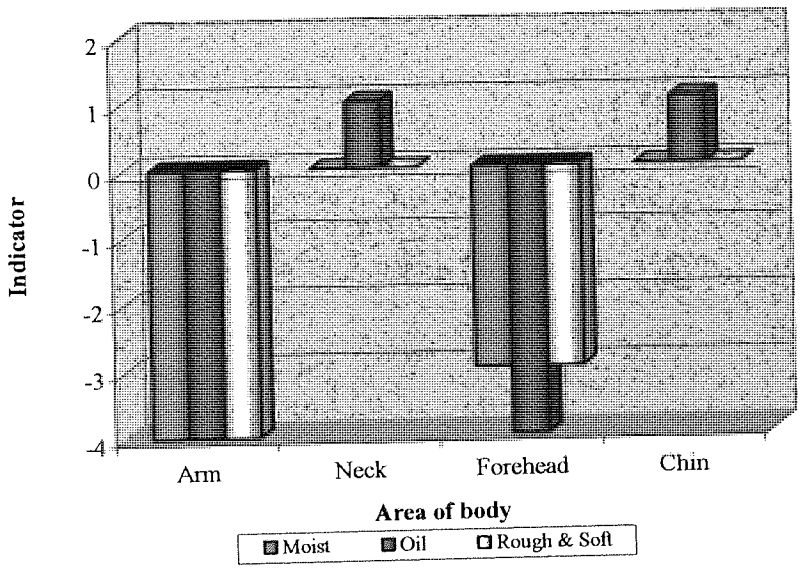


Figure 7.11 Skin Reader values of different areas of the body

The skin on the forehead contained a slightly higher amount of moisture than the forearm, but was still classified as being dry. This highlights that different parts of the body have subtle differences in moisture which result in combination skin. Therefore, it is essential to use the same conditions for testing. By trying to achieve specific conditions from physical interventions, will give rise to results that do not show the full potential of the moisturisers to be investigated in later sections.

Further tests were carried out to highlight the effects that various types of moisturisers or chemicals have when applied topically to the forearm. Figure 7.12 shows blank reading taken before the chemicals were rubbed into the skin. Moisture promoting agents were rubbed into the skin and left for an hour before being tested with the skin reader MY-610. Four readings were taken and the average values were displayed. The results highlighted that the skin on the forearm is adequately moisturised through natural control mechanisms which is classified as normal skin. The addition of neat glycerol to the skin resulted in the decrease of the moisture content of the skin and also the softness of the test site. The skin is classified as possessing a normal level of moisture content. However, the reduction occurs from the interaction of the glycerol with the water. The amount of free water is ultimately reduced through hydrogen bonding. The hydrophilic humectant does not interfere with the amount of the lipophilic oil within the skin, hence this value remained static.

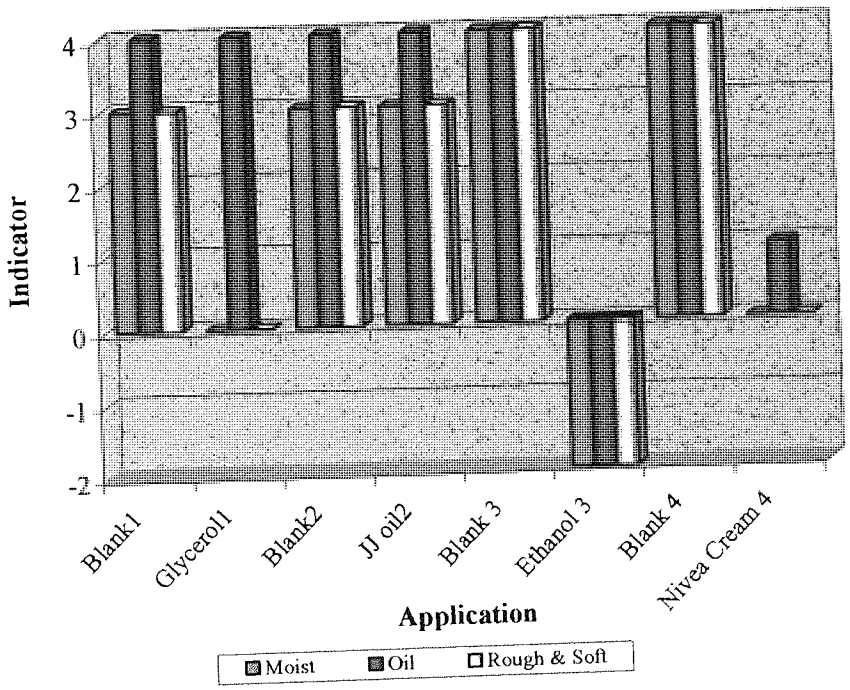


Figure 7.12 Skin Reader Values of different types of moisturiser

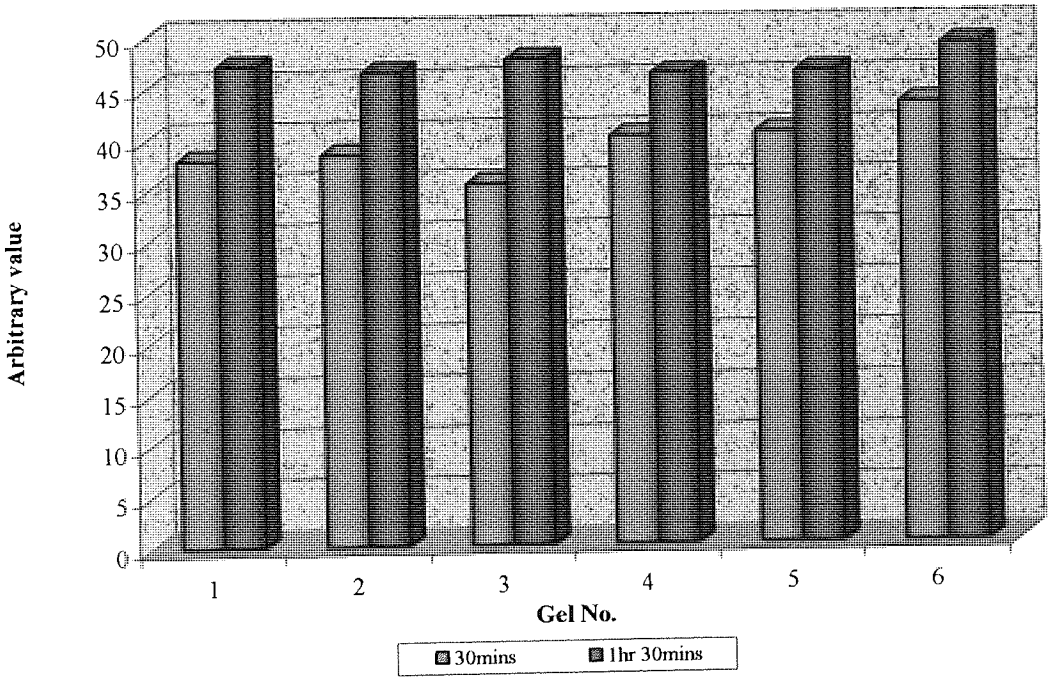
The addition of neat Jojoba Oil to the skin showed no changes in the levels of moisture, oil or softness of the skin after an hour. The amount added to the skin was absorbed into

the lipid layer of the stratum corneum without leaving a greasy residue. Jojoba oil is well known as a mimic for sebum. When used in small quantities it can provide the properties expected from well moisturised, supple skin, without causing other skin conditions when using other types of oils. The addition of ethanol to the skin was used to illustrate that this chemical is well known for removing the hydrophobic matter of the skin, which would in turn cause disruption of the aqueous matter contained within the corneocytes. This resulted in the substantial decline in the moisture, oil and the softness of the skin, which is provided by the former two components.

Addition of Nivea cream to the skin resulted in a reduction of the moisture and oil constituents. However, it was still classified within the normal skin range. Ideally, the addition of a preformed O/W emulsion should increase these values dramatically. Glycerol interacts with the water within the stratum corneum. Active agents within the moisturiser reduce the amount of moisture within the skin. The level of oil decreases due to the level of surfactants contained within this preformed active agent containing emulsion. Moisturisers are known for containing humectants for example glycerol and PCA. Essentially they interact with the water via hydrogen bonding. Unfortunately, the levels of surfactant possess the potential to disrupt the organisation of the lipid layers with the stratum corneum. Ideally, skin adhesive hydrogels containing less surfactant can be employed as the delivery matrix whilst minimising the disruption of skin lipids.

7.4.5 In Vivo Release Analysis Using the Corneometer CM-825

Vitamin B5 a water soluble active agent is well known for its humectant properties and therefore it was incorporated into monophasic skin adhesive hydrogels. Figure 7.13 shows the level of skin hydration measured using the corneometer. Gels containing lipophilic actives were not used in these release studies, since they could potentially interfere with the electrode probe causing irreversible damage. Therefore, only water soluble actives were released and ten skin measurements taken with the average values displayed. A blank reading was taken of the skin before any tests were conducted giving a value of 32.4 arbitrary units.



Gel No. 1: *NaAMPS only*

Gel No. 2: *NaAMPS/ AMO*

Gel No. 3: *NaAMPS/AMO/ 1% w/w D-Ca Panto*

Gel No. 4: *NaAMPS/AMO/ 2% w/w D-Ca Panto*

Gel No. 5: *NaAMPS/AMO/ 3% w/w D-Ca Panto*

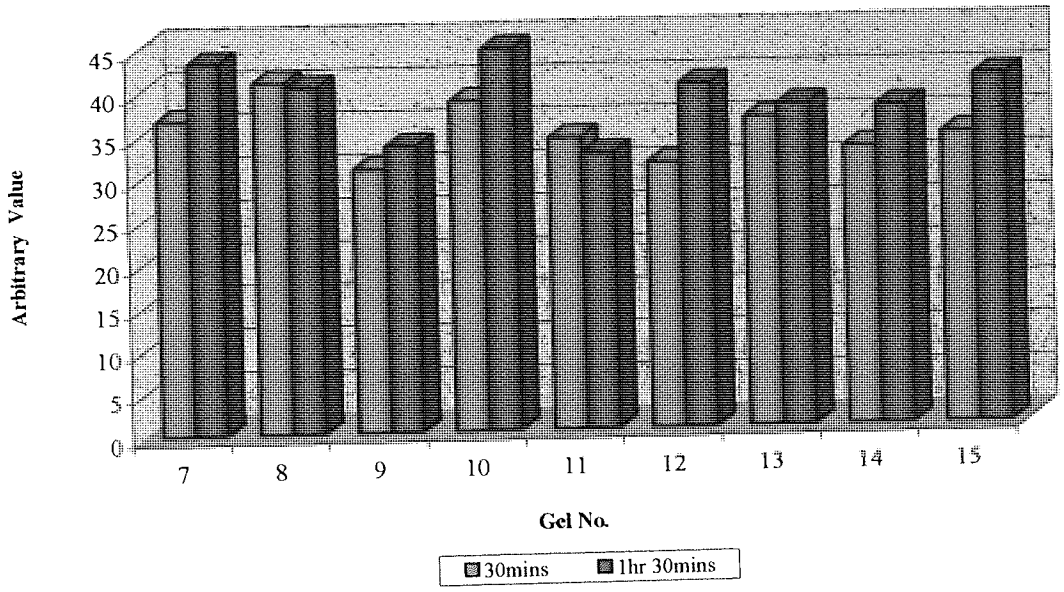
Gel No. 6: *NaAMPS/AMO/ 4% w/w D-Ca Panto*

Figure 7.13 Monophasic hydrogels containing no actives or D-Calcium Pantothenate an active agent

The results highlight that the monophasic gels composed of poly NaAMPS or poly NaAMPS –co-AMO increase the hydration of the skin over thirty minute or one and a

half hour time periods. The equilibrium water content of the gel is higher than that of the skin, therefore water is driven by osmosis from the gel until a state of equilibrium is achieved. In general, the release of the water soluble active agent d-calcium pantothentate increases the hydration content of the skin and has the ability to hydrogen bond with the water already present within the stratum corneum. Water that is driven from the skin adhesive in order to achieve equilibrium increases the levels of hydration. The active agent is a humectant, which has the ability to retain water within the skin. This results in higher values of hydration when compared to the gels containing no actives. After an hour and thirty minutes the values reached approximately 45 arbitrary units showing that the skin had reached adequate moisturisation in this short time span.

The results displayed in figure 7.14 are release studies from biphasic skin adhesive hydrogels containing 0, 0.25 or 1.00 % w/w of PCA. The skin adhesive hydrogels containing no actives increased the hydration of the skin due to the release of water from the polymer matrix. The gel also forms an occlusive covering which promotes an increase in moisture. All of the gels have the potential to increase the hydration of the skin when taking into consideration that the release was carried out for a short period of time. The primary NMF was released in low quantities and since it had to travel through the polymer matrix via the sites not containing the lipoidal phase on the surface, this reduced the rate of release. The PCA was released but as shown in a previous chapter due to the phase distribution the quantities released did not always follow a trend of increased hydration with an increase in the amount of active agent. Another possible suggestion for this reduced hydration could be that the water within the skin had hydrogen bonded to the PCA. More water could potentially be obtained from the atmosphere, but realistically from the deeper layers of the skin, when it migrates from deeper underlying layers. During the initial thirty minutes of testing some of the gels withdraw water from the skin trying to strive for an equilibrium water content between the skin adhesive hydrogel and the skin. Experiments carried out for one hour and thirty minutes generally resulted in an increase in the hydration of the skin since the gel was given more time to release the PCA. These gels resulted in increased hydration values, but were dependant on the positions of the hydrophobic phase within the three dimensional polymer matrix.



Gel No. 7: *NaAMPS/AMO/ESBA no active*

Gel No. 8: *NaAMPS/AMO/ESBA 0.25%w/w PCA*

Gel No. 9: *NaAMPS/AMO/ESBA 1.00%w/w PCA*

Gel No. 10: *NaAMPS/AMO/LA no active*

Gel No.11: *NaAMPS/AMO/LA 0.25%w/w PCA*

Gel No. 12: *NaAMPS/AMO/LA 1.00%w/w PCA*

Gel No. 13: *NaAMPS/AMO/SA no active*

Gel No. 14: *NaAMPS/AMO/SA 0.25%w/w PCA*

Gel No. 15: *NaAMPS/AMO/SA 1.00%w/w PCA*

Figure 7.14 Biphasic hydrogels containing no actives or PCA the primary NMF

Tests were conducted after the results stated above were recorded. A slight decrease in the water content of the skin was observed. This highlighted that the addition of only water soluble NMFs would not suffice to maintain the moisture levels of normal skin. An occlusive layer is essential to keep the water soluble active locked within the stratum corneum so they can fulfill their role or until water migrates from the underlying layers of the stratum corneum.

7.4.6 In Vivo Release Monitoring Using Tape Stripping in Conjunction with FT-ATR

The FT-ATR spectra gave valuable information which was used to understand the basic composition of the stratum corneum. An alkane stretch at 2853cm^{-1} was due to the presence of a sp^3 C-H, an ester stretch at 1740cm^{-1} and an alkane $-CH_2$ deformation bend 1460cm^{-1} represented the lipids present in the skin. The proteins were represented by an N-H stretch at 1480cm^{-1} and C-O at 1160cm^{-1}. The majority of bands present are due to the major components of skin, lipids and proteins. However, an area of importance for these studies was the O-H stretching region located at a frequency of approximately 3200cm^{-1}.

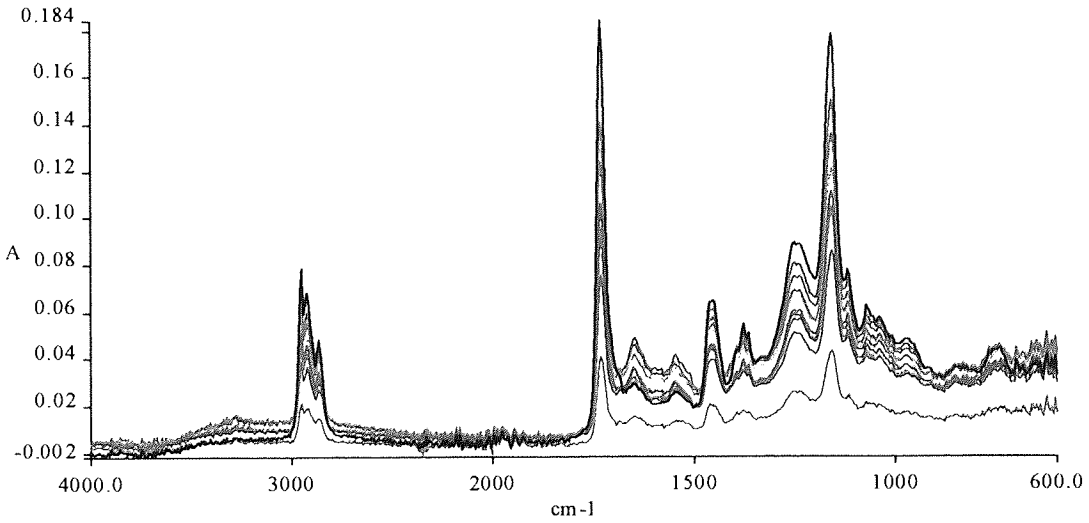


Figure 7.15 FT –ATR Traces of Tape Stripped Stratum Corneum

When an increase in the water content of the skin occurred it ultimately resulted in an increase in the absorbance of the O-H stretch band. Figure 7.15 shows the moisture at an optimum level and higher absorbance values which can be correlated to an increase in the moisture content of the stratum corneum. Figure 7.16 shows the absorbance values at selected frequencies in different tape strips. They show that as the layers of the stratum corneum are removed the water content remained approximately static, highlighting that the skin has reached its optimum level and that it was not dehydrated. The absorbances

of the ester group of the lipids at 1740cm^{-1} and proteins C-O stretch at 1160cm^{-1} give higher values than those of the water content.

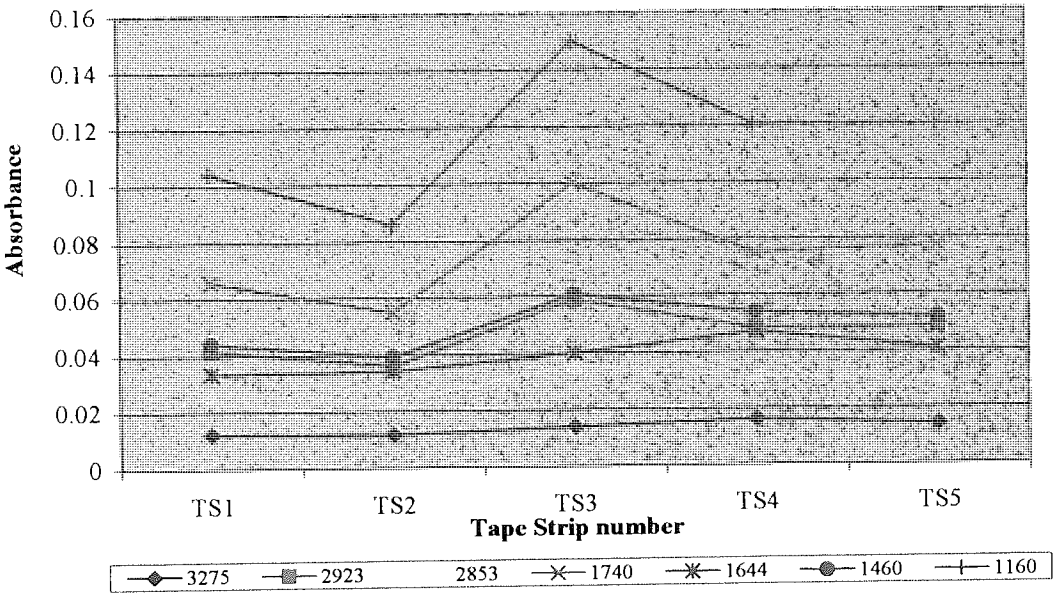


Figure 7.16 Blank Tape Stripping of the Stratum Corneum

Figure 7.17 shows that the application of neat jojoba oil does not alter the moisture content of the stratum corneum. The change in absorbance at 3275cm^{-1} is similar as the number of tape strips increases. Comparison of these results with those in figure 6.16, show that the jojoba oil has been absorbed by the stratum corneum. Increases in the lipid absorbance values were observed, as expected, this fatty ester naturally increases the content of the carbonyl and hydrocarbon groups within the stratum corneum. A higher quantity of lipid was present within the first layer tape stripped with elevated amounts within the other layers. The lipid had traveled deep into the stratum corneum which was evident by the absorbance values obtained. Figure 7.18 showed the tape stripping results achieved after an O/W moisturiser had been rubbed into the stratum corneum, on the forearm. The water content of the stratum corneum had increased considerably in the layers tape stripped 1-4. After this point, the water content decreased but it was still higher than the blank value showing that the moisture within the stratum corneum had not equilibrated. Nivea cream increased the lipid and protein component of the skin highlighting that the ingredients had penetrated through the stratum corneum increasing

the moisture and the hydrophobic component. These vital elements are essential for the achievement of soft, supple adequately moisturised skin.

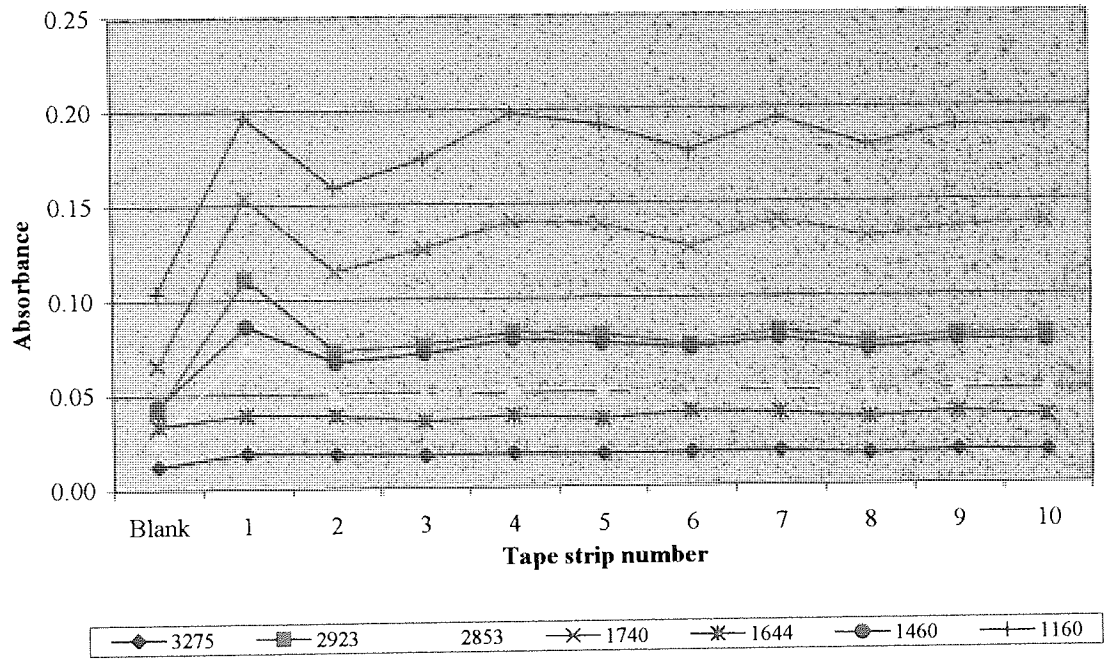


Figure 7.17 Tape Stripping of the Stratum Corneum moisturised with Jojoba oil

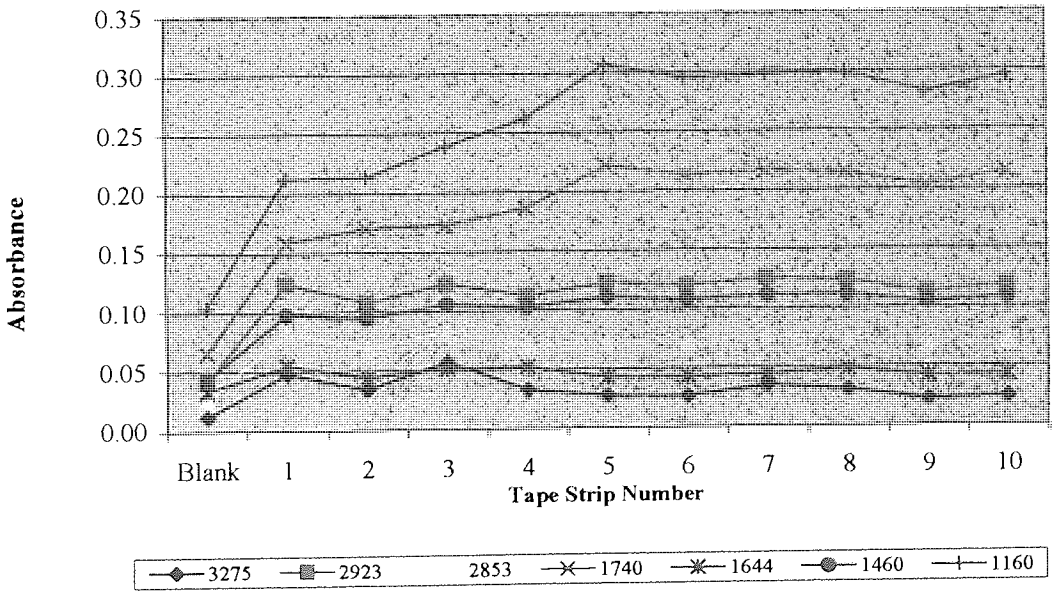


Figure 7.18 Tape Stripping of the Stratum Corneum moisturised with Nivea Cream

7.4.7 In Vivo Release of PCA From Monophasic and Biphasic Technology Hydrogels

This section investigated the release from a monophasic technology skin adhesive loaded with 1% w/w PCA and a biphasic technology hydrogel loaded with either 1 % w/w PCA or a combination of 1% w/w PCA and 1% w/w of Vitamin E.

Release studies were conducted on the authors arm with the removal of the monophasic or biphasic gels after one or three hours. The skin was tape stripped and analysed by FT-ATR. Figure 7.19 highlights the differences between treated and untreated skin. The absorbance values at 3275cm^{-1} gave an indication of the hydration level of the skin. Untreated skin gave an absorbance of approximately 0.01, showing that a low amount of water was present. After an hour the hydration level had increased to 0.05 and after three hours it was above 0.60. The water content within the top layers of the stratum corneum was similar to those at lower levels. PCA was released from the skin adhesive which traveled through the stratum corneum, illustrated by an increase in the absorbance level. An increase in the level of hydration was observed when the gel was left on the skin for three hours.

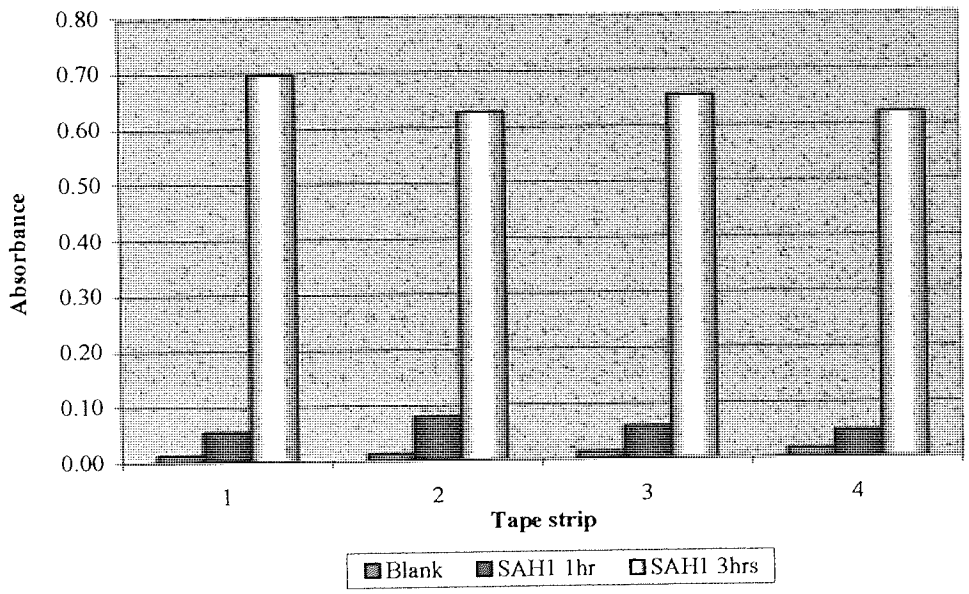


Figure 7.19 Release of PCA from a monophasic hydrogel

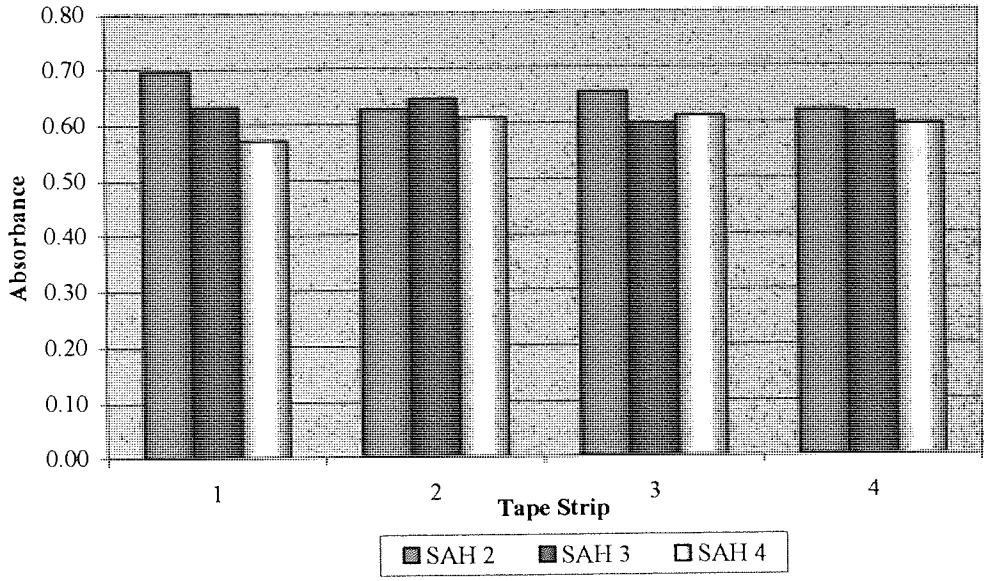


Figure 7.20 Release of PCA from monophasic and biphasic hydrogels after 3 hours

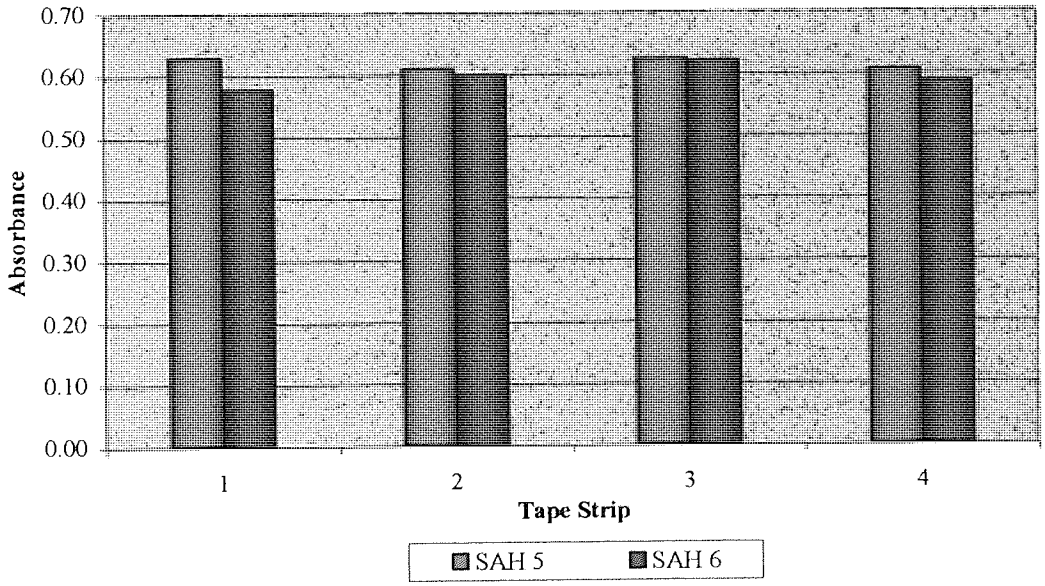


Figure 7.21 Release of PCA & Vit E from biphasic hydrogels after 3 hours

SA2, SA3 and SA4 were monophasic, biphasic and O/W emulsion biphasic technology gels respectively. They were loaded with 1 % w/w PCA. The results showed that despite possessing different chemical compositions, the gels released similar amounts of PCA. The stratum corneum was successfully hydrated and the tape stripping proved that the PCA had penetrated through it.

Gels SA5 and SA6 contained a hydrophobic polymer (poly LA) and Flexbond 150 respectively. The gels were loaded with 1% w/w PCA and 1% w/w Vitamin E. The absorbances recorded were similar to the gels containing only PCA. The incorporation of Vitamin E did not hinder the release from the gel. Release of both actives promoted the hydration and softness of the skin.

PCA is the primary moisturising factor found within skin. These gels can release adequate amounts of PCA, however, this will rectify the problem of dehydration. Vitamin E provides and occlusive barrier on the skin, preventing the loss of essential moisturisers.

7.5 Discussion

The in vitro and in vivo release of hydrophilic and hydrophobic actives was investigated. In vitro release using an aqueous and lipoidal mimic, poly HEMA and silastic respectively, provided qualitative information about the concentrations of PCA, LA and Vitamin E released. Monophasic skin adhesive hydrogels allowed the incorporation of hydrophilic actives ranging from high water solubility LBA to lower solubility PCA. The results highlighted that PCA could be partitioned in both the aqueous and lipoidal mimics. This NMF was released from the three dimensional polymer matrix and possessed the potential of passing through the lipoidal and aqueous sections of the stratum corneum. An identical monophasic vehicle can essentially be used for the release of a range of hydrophilic actives possessing different log K_{ow}, values, making this technology transferable. Incorporation of PCA into a biphasic gel containing Vitamin E resulted in higher quantities of the latter being released, due to its location. It was predominantly located at the surface. However, the quantity of PCA released enabled the stratum corneum to be sufficiently moisturised.

The incorporation of a poly hydroxy acid, lactobionic acid showed excellent antioxidant properties at concentrations less than 1% w/w. Widely available antioxidants are lipophilic (Vitamin A or E) and therefore they require a different type of technology to incorporate them within polymer matrixes. This chemical has multiple roles, not only is it an antioxidant but it can be used to chelate iron within the skin, reducing the signs of ageing. It has tremendous potential to hydrogen bond with water, promoting the moisture content of the skin. A simple yet highly effective method of release of the LBA from within monophasic gels, were conducted using banana peel as the release substrate. Usually the peel discolours within a few hours due to oxidative degradation. LBA interfered with the oxidative degradation of the peel. It was prolonged for forty hours. At this stage the onset of degradation had initiated. This type of active agent has the potential to be an anti ageing active and a preservative.

In vivo tests were carried out on the author's forearms and measurements were taken using a skin reader MY-610, a corneometer CM825 or tape strips analysed by FT ATR. The skin reader measured the moistness, oiliness and the softness/ roughness of the skin. This machine was used to highlight that different parts of the body possess different levels of hydration and suppleness. The forearm was selected since less natural oil sebum was present which would potentially interfere with the release studies and give inaccurate values of hydration. The corneometer was used to measure the hydration of the skin and the results achieved showed that the skin was moisturised using the water soluble active agent d-calcium pantothenate and PCA. However, the aqueous component alone cannot rectify the inadequate hydration of the skin. It is essential that a lipophilic component either vitamin E or jojoba oil are released. They form an occlusive barrier, trapping the moisture within the skin allowing the body to naturally produce moisture deep within the underlying layers. This reduces the probability that the stratum corneum will breakdown, leaving it open to bacteria and allergens.

Tape stripping used in conjunction with FT-ATR provided valuable information on the main components in the stratum corneum – lipids and proteins. The area of importance was the region where the O-H stretching vibration was located, at approximately 3200 cm^{-1}. Absorbance values at this frequency were compared to see if hydration had occurred. The addition of jojoba oil to the stratum corneum did not result in an increase in the moisture content as shown by the results displayed in figure 7.17. The lipid content within the stratum corneum increased and was reflected in the absorbances displayed at the corresponding frequencies. The application of an O/W emulsion cream resulted in an increase of the hydrophobic content and the hydrophilic content of the stratum corneum. It is essential to incorporate both hydrophilic and hydrophobic components, in order to restore the natural balance of the stratum corneum. Monophasic and biphasic gels containing 1% w/w of PCA increased the hydration levels of the stratum corneum after three hours. This highlighted the potential of these vehicles to deliver active agents and the potency of the NMF in promoting the hydration of the skin.

Chapter 8

Conclusions & Further Work

8.1 Overview

This thesis investigated the development of tailor-made, partially hydrated, skin adhesive hydrogels as a vehicle for topical delivery. The focus was placed upon the synthesis of three dimensional polymer networks possessing good cohesive and adhesive properties. Skin adhesives based upon monophasic technology were investigated to determine fundamental factors. Understanding the basic principles of photopolymerisation and gel technology enabled modifications to be implemented for specific applications.

The incorporation of a suitable monomer possessing a high degree of lipophilicity to a predominantly hydrophilic based pregel, gave rise to biphasic gel technology. An alternative method used to introduce the hydrophobic component was via the addition of an O/W emulsion. The compositions were manipulated to ensure that the hydrophobic content did not have a detrimental effect on the mechanical properties of the gel.

A range of active agents were selected to maintain an adequate level of hydration of the stratum corneum. The appropriate gel technology was chosen to accommodate the active agent. In vitro release studies were conducted using silastic and polyHEMA as the lipoidal and aqueous mimics respectively of the stratum corneum. In vivo release studies were conducted on the authors arm using a range of techniques to measure the aesthetic quality and hydration levels of the skin.

8.2 Photopolymerisation and Partially Hydrated Monophasic Gel Technology

Partially hydrated monophasic hydrogels composed of an unsaturated ionic monomer NaAMPS, a humectant, glycerol and plasticiser, water were converted into a three dimensional polymer matrix. Unsaturated monomers were converted to their corresponding polymers by photopolymerisation. Primary free radicals were formed when the photoinintator was decomposed.

An adequate supply of free radicals will not result in the formation of a three dimensional polymer matrix. A bifunctional monomer/ polymer must be present in the pregel solution. This chemical has the ability to link monomer units together through covalent interactions, producing a three dimensional polymer matrix. The structural integrity of the gel alters when an excessive amount of crosslinker is incorporated into the formulation, resulting in a rigid polymer, unable to conform to the contours of the skin.

Partially hydrated skin adhesive hydrogels containing poly NaAMPS-co-AMO are more cohesive and adhesive than the corresponding poly NaAMPS gels. Peel strengths of the latter gels possessed half the values of those containing AMO. The presence of the non ionic monomer AMO increases the cohesive and adhesive strength through hydrogen bonding with suitable components within the gel.

Greasy skin interferes with the attachment of a partially hydrated adhesive hydrogel by rendering monophasic gels non adhesive. This problem was rectified by adding non ionic block copolymeric surfactants P65 to monophasic pregel formulations. The surfactant encapsulates the excess oil within the hydrogel matrix. Rheological studies confirmed that skin adhesives containing between 0.1 and 0.5 % w/w of P65 possessed similar elastic and viscous moduli at low and high shear rates when compared to the monophasic gel containing no surfactant. At high levels of P65 (greater than 2.0 % w/w) the structural integrity of the monophasic gel was compromised. These types of gels increase the risk of skin irritation.

Exploitation of monophasic gel technology enabled the synthesis of tailor-made skin adhesives. Non ionic poly AMO gels have a lower affinity to water and exhibit less swell, when compared to poly NaAMPS gels. This type of gel has the potential application as an ostomy adhesive. The AMO based pregels had a low viscosity. This caused complications at the coating stage, before photopolymerisation was initiated. The addition of PQ4 increased the viscosity of the pregel and the peel strength, when compared to monophasic gels containing no PQ4. The cohesive strength was enhanced through the hydrogen bonding between AMO and polyquaterium 4.

8.3 Fully Hydrated Non adhesive Biphasic Hydrogels

Preliminary synthetic studies showed that a bulky hydrophobic monomer, ESBA could be copolymerised with both HEMA or N,N DMA. Pale yellow, brittle gels were formed. For certain applications (e.g. a wound site), transparent gels are required. Therefore, large quantities of ESBA would inevitably compromise the visibility of the underlying site of attachment.

Gels synthesised using thermal or UV initiators gave similar equilibrium water contents. PolyN,N DMA containing hydrogels, yielded double the EWC values of polyHEMA gels. This highlighted that polyN,NDMA was more hydrophilic. As the quantity of hydrophobic matter was increased, a reduction in the EWC occurred due to the reduction in the hydrophilic monomer, which provided the sites where water could hydrogen bond.

8.4 Partially Hydrated Biphasic Gel Technology

Utilisation of monophasic skin adhesive technology enabled the development of biphasic skin adhesives. A hydrophobic monomer was distributed throughout a three dimensional hydrophilic polymer matrix gave rise to this type of technology. This new gel system was designed because monophasic gels can only release hydrophilic actives. A gel that permitted the incorporation of both hydrophilic and hydrophobic actives was synthesised.

ESBA was selected as the hydrophobic monomer due to its low toxicity and pleasant odour, which made it acceptable to work with in a laboratory. A bridging monomer was required to bring the hydrophilic and hydrophobic components of the pregel together, forming a homogeneous solution. AMO was the most suitable bridging monomer due to the adequate interactions with both hydrophobic and hydrophilic components. Hydrogen bonding with other hydrophilic chemicals increased the adhesive and cohesive properties of the gel.

The stability and distribution of the hydrophobic monomer within the pregel was enhanced by the addition of no more than 1 % w/w of Tween 20 or Tween 60. Low quantities of this non ionic surfactant were selected due to their compatibility within the gel and with the skin. Elevated quantities interfered with the adhesive strength of the skin adhesive. An increase in the quantity of surfactant resulted in the increase of the hydrophobic content of the gel which changed its structural integrity.

The addition of an alternative hydrophobic monomer (e.g. butyl acrylate, lauryl acrylate or stearyl acrylate) to the pregel, resulted in an even distribution when compared to the bulky ESBA. Gels containing butyl acrylate were subjected to gamma radiation, which eliminated the odour, indicating the reduction of unpolymerised monomer. However, preparation of the pregel was a major issue therefore lauryl and stearyl acrylate were selected as suitable alternatives.

Biphasic gels containing ESBA, LA or SA possessed lower peel strengths than their monophasic equivalents. The hydrophobic component was found predominantly at the surface of the biphasic gel. Rheological studies determined that these gels possessed the prerequisite structural integrity, required by viscoelastic gels. At low and high shear stresses the elastic modulus was greater than the viscous modulus, showing that the gel could be applied and removed in one piece, without leaving residue.

8.5 Partially Hydrated Biphasic Gel Technology Containing an O/W Emulsion

An alternative method used to introduce the hydrophobic component to a predominantly hydrophilic pregel, involved the incorporation of a preformed commercial O/W emulsion. Incorporation of an unsaturated hydrophobic monomer requires specialist preparation, to ensure that a homogenous pregel solution was achieved. Commercial preformed emulsions were added since the hydrophobic component is dispersed and stabilised throughout the water phase.

The addition of an O/W emulsion to a NaAMPS pregel, resulted in its destabilisation and agglomeration at room temperature. When AMO was added to the preformed O/W emulsion it located itself around the latex particles, increasing their hydrophilicity. Water was strongly attracted, creating a protective water barrier between them, which prevented coagulation.

Glycerol aided this process by allowing the slow addition of NaAMPS, ensuring that the AMO was not displaced. If the speed of mixing exceeded 250 revs per min, this pregel system destabilised. A temperature in excess of 70°C compromised the stability of the emulsion. The optimum conditions for preparing these types of pregels were deciphered from preliminary studies to be 50°C with mixing at 100 revs/min.

Incorporation of 5 % w/w DM137, Flexbond 150 or Texicryl 13056WB to a monophasic pregel resulted in the adhesivity of the gel increasing when compared to those containing no O/W emulsion. The cohesive and adhesive strength increased with an increase in hydrophobic content. Gels containing 5 % w/w of Texicryl 13056WB had a stronger adhesive bond than compared to Flexbond 150 or DM137. The emulsions behaved in accordance with their chemical structure and their environments. Due to their range of hydrophobicity they interacted with pregel components to different degrees.

A high level of an O/W emulsion was regarded to be 25 % w/w, which resulted in opaque gels. They possessed a lower adhesive strength compared to those gels containing 10 % w/w. The cohesive strength and structural integrity had not been compromised. Lower quantities of the emulsion interact with the components in the pregel enhanced the physical properties of the gel. However, amounts added in excess of 10 % w/w restricted molecular motions, reducing the potential skin contact and the adhesive bond strength between the substrate and the gel.

From a synthetic perspective, Flexbond 150 was incorporated with ease when compared to Texicryl 13056WB. The application determines the level of adhesion required by a gel to fulfill its role. However, 4 % w/w of emulsion can be used in conjunction with 2.8 %

w/w of acrylic acid which approximately doubles the peel strength of a gel. The water binding potential within the gel is increased by the interactions between the acrylic acid and hydrophilic components, through hydrogen bonding. This allows rotation of polymer chains increasing intermolecular interaction for example between two NaAMPS the sulphonate amide group.

Rheological studies of hydrogels containing O/W emulsions showed that the elastic and viscous moduli were lower than those results obtained for a monophasic gel at low and high shear stresses. An increase in the hydrophobic content, affects the mechanical properties of the gel, due to the restrictions imposed by them. The Tan δ values for these gels were below 1, showing that despite having lower elastic and viscous moduli they were classified as viscoelastic materials.

Non ionic gels containing 0.3 % w/w of PQ4 and Flexbond 150 or DM137 gave higher peel strengths than those containing 0.3 % w/w of PQ10. The reduction in the adhesive strength is due to the presence of the hydrophobic PQ10. The range of gels synthesised can be used for a variety of applications and have the potential to release actives.

8.6 Incorporation of Active Agents

The log K_{ow} values gave a good indication of the solubility of an active agent and allowed the appropriate gel technology to be selected. Highly hydrophilic actives d-calcium pantothenate and lactobionic acid have log Kow values of -5.35 and -4.89 respectively. They were soluble within monophasic gel technology. When 4 % w/w of d-calcium pantothenate was added to a monophasic pregel it resulted in the increase of hydrogen bonding within the gel. An increase in the elastic and viscous components highlighted that the molecular motion within the gel was restricted, when compared to a gel containing lower quantities of the active.

Lactobionic acid increased the peel strength of the skin adhesive hydrogel and did not interfere with the elastic and viscous components of the gel. This type of active was ideal,

since it promoted adhesion and was a well known hydrophilic moisturiser. It will aid that the maintenance of the optimum level of hydration. Monophasic gel technology allows the incorporation of hydrophilic actives. This limitation arises from the predominantly hydrophilic pregel components and cannot accommodate hydrophobic actives.

Approximately 2 % w/w of PCA could be incorporated into the monophasic gels, before insolubility occurred. Incorporation of PCA to a biphasic technology pregel solution, allowed it to be dissolved, forming a homogenous mixture. The active agents added must possess the characteristics required by a moisturising agent. DVS studies showed that PCA absorbed moisture as the humidity was increased and did not relinquish it when the humidity was decreased. Lactobionic acid and d-calcium pantothenate absorbed more, water but they could not retain it when the humidity was lowered.

The hydrophilic and hydrophobic phases of a biphasic technology gel can be utilised to allow the incorporation of actives with a range of solubilities. Jojoba oil was successfully incorporated into the gels in conjunction with PCA the primary NMF. Less than 2 % w/w of a hydrophobic agent ensured that the structural integrity of the gel was not compromised. Release of a combination of actives would enable the different degrees of dry skin to be alleviated.

8.7 Release Studies from Partially Hydrated Skin Adhesive Hydrogels

In vitro studies were conducted with polyHEMA and silastic as the hydrophilic and hydrophobic mimic of the stratum corneum respectively. The results highlighted that PCA and LA could be partitioned in both phases but were predominantly found in the aqueous phase. This type of experiment highlighted that these water soluble active agents could be released from monophasic technology gels. Ultimately the size, structural affinity, log K_{ow} and the charge of the actives determine if they will be released from the three dimensional polymer matrix. The log K_{ow} value of the active agent gives as good indication to the appropriate gel technology.

The commercial uses of lipophilic antioxidants are of importance and require specialised vehicles for delivery. Lactobionic acid has shown that it participates in numerous roles when released into skin. This water soluble active agent is potent at 1 % w/w and maintains this role for approximately forty hours, when released from a monophasic hydrogel. 'Burst release' was the mechanism by which the active agent exited the gel, followed by the continual replenishment from the three dimensional polymer matrix, until it reaches it limit. Banana peel has proven to be an ideal model for assessing the release of the lactobionic acid which highlighted its potential as a water soluble antioxidant.

In vivo studies of the stratum corneum were successfully conducted using a range of techniques. Non invasive tests were implemented with the aid of the Skin Reader MY-610 and the Corneometer CM825. Invasive tests of the stratum corneum involved analysis using FT-ATR. These three techniques provided information about the moisture, aesthetic quality and levels of oil present in the top layer of the skin. The moisture levels of skin can differ for a number of reasons including type, diet, washing and moisturising regimes.

The release of d-calcium pantothenate from a monophasic technology gel demonstrated an increase in the moisture content of the skin. The Corneometer CM 825 provided the skin moisture values and enabled any increase or decrease in the level of hydration to be detected. Biphasic gels containing PCA showed a slower rate of release compared to the release of the hydrophilic active d-calcium pantothenate. The major difference was the composition of the gels. The presence of a hydrophobic phase throughout the gel and which is particularly concentrated on the surface results in the reduced rates of hydrophilic actives when compared to those released from monophasic gels.

Tape stripping of the stratum corneum analysed by FT-ATR provided information about the degree of moisturisation within this layer. Primary area of interest for these studies was the O-H stretching region located at a frequency of approximately $3200cm^{-1}$. A simple comparison between an O/W moisturiser (Nivea Cream) and an emollient (jojoba oil) showed that it is essential to have a combination of both hydrophilic and hydrophobic

components to ensure that the skin was provided with moisture. The hydrophobic component ensured that an occlusive layer does form which reduces the rate of evaporation. The release of actives PCA from monophasic and biphasic hydrogels increased the moisture content of the skin. FT-ATR provided invaluable information about the stratum corneum. These gels can rectify mild dry skin conditions within three hours when applied to the required site.

8.8 Concluding Summary

Extensive studies were undertaken to design and synthesise novel partially hydrated skin adhesive hydrogels, for the topical delivery of active agents. This thesis was directed towards an application which potentially addressed inadequate hydration of the skin. An array of gels were synthesised with focus placed upon monophasic and biphasic technologies.

Monophasic technology gels were synthesised using an unsaturated hydrophilic monomer NaAMPS, a humectant glycerol, plasticiser water, a photoinitiator Irgacure 184 and a crosslinker Ebacryl II. Synthetic studies led to the development of poly NaAMPS-co-AMO hydrogels possessing improved cohesive and adhesive properties. Biphasic gels containing ESBA, LA and SA were synthesised which yielded different dimensions of the hydrophobic phase throughout the hydrophilic polymer matrix. Gels containing NaAMPS, AMO and LA had an even distribution of the latter polymer throughout the matrix. This was controlled by the type of surfactant, the speed of mixing and the temperature at which the pregel was prepared.

The development of the biphasic gels led to the replacement of hydrophobic monomers with commercial O/W emulsions. The peel strength of the gels increased at low concentrations when compared to monophasic gels containing no emulsion. The presence of this type of hydrophobic monomer allowed the incorporation of actives with ease. Structural integrity was maintained, highlighting that the vehicle was viable as a skin adhesive.

8.9 Suggestions for Further Work

This thesis investigated the synthesis of a range of novel skin adhesive hydrogels, as a vehicle for the topical delivery of natural moisturising factors and lipoidal actives. Numerous areas were considered and exploited in order to determine the potential of monophasic and in particular the biphasic gels. Initial studies were focused upon the synthesis of monophasic skin adhesives, which provided fundamental information. The limitations posed by these gels led to the development of biphasic skin adhesives. These technologies highlighted that actives with a range of solubilities could be incorporated.

Synthesis of monophasic hydrogels were predominantly directed toward the incorporation of the ionic monomer, NaAMPS. Gels were synthesised using the non ionic monomer AMO and a polyquaterium, PQ4/PQ10. The synthesis of skin adhesives using other ionic monomers and non ionic monomers should be investigated to enable the development of monophasic technology. The polymeric interactions within the gel should be studied to understand the cohesive properties of the gel.

It was essential to incorporate a viscosity modifier to monophasic gels. Coating of the pregels containing this chemical enabled the formation of uniform gels. Understanding how they enhance the cohesivity, adhesion and viscosity of the gel should be considered by incorporating the appropriate water soluble polymers. Less than 0.3 % w/w increased these properties. The molecular motions within biphasic gels should be limited to reduce the probability of phase separation, when incorporating more than 10 % w/w of an unsaturated hydrophobic monomer.

Non ionic surfactants were added to biphasic hydrogels containing unsaturated hydrophobic monomer. This class of surfactant was selected due to its low toxicity and compatibility with the skin. Polymerisable surfactants should be investigated to establish their compatibility within the pregel. It was imperative that the size of the hydrophobic domain and stability of the micelle are controlled to enable an even distribution

throughout a three dimensional polymer matrix. The toxicity of the surfactant must be determined to ensure that it does not have an adverse effect within the skin.

The hydrophobic component was added in the form of an O/W emulsion, which provided skin adhesives with good cohesive and adhesive properties, when no more than 5 % w/w was incorporated. Novel O/W emulsions can be synthesised using ESBA, which would allow highly hydrophobic actives to be incorporated. The factors affecting the adhesive and cohesive properties need to be investigated, using a wide array of emulsions. The precise mechanism which allows these changes to occur must be established.

Actives were incorporated into skin adhesive hydrogels and the limitations of monophasic technology gels were established. They have the potential to accommodate hydrophilic and hydrophobic actives at low concentrations. PCA the primary NMF and Vitamin E were used to induce moisturisation. The lipophilic component was added to form an occlusive layer over the skin. Different combinations need to be investigated to ensure that potent combinations are delivered to rectify dry skin.

Cross polarisation magic angle spinning solid state NMR studies of partially hydrated skin adhesive hydrogels were investigated. This technique provided information about the chemical composition and unfortunately all of the peaks were not collected. This technique should be pursued to understand how the chemicals interact within the three dimensional polymer matrix. A specialist technique is required since the gels cannot be dissolved in any solvent.

In vitro release tests enabled the quantities of the active agent to be monitored. However, in vivo studies gave more realistic data and allowed the physical effects of the actives to be measured. The authors arm was used to carry out the release studies. It would be advisable to have a range of subjects available with different degrees of dry skin. This would allow the correct quantities and combinations of actives to be established which could rectify dry skin.

Studies on different types of skin would provide information to enable the appropriate active to be selected, which would aid the repair of dry skin. Establishing the different types of skin is a vast area of research. It is essential that different people with different extents of dry skin be tested to enable the effectiveness and the length of time it takes to correct the problem.

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