# CHAPTER 2

# Hydrogels for Use as Wound Dressings for Second Degree Burns

## 2.1 Introduction

Historically, many different types of material have been developed to treat burns. One such natural material which is well known is *aloe vera*. The extracted natural hydrogel has been used as a burn dressing for hundreds of years but it is limited to only first degree burns. Physiological dressings and lyophilised pigskin have also been used but they need to be changed after a very short time. More recently, biological dressings (e.g., amniotic membranes) have been developed but the high risk of HIV infection is a major disadvantage. Collagen has also been used to treat burns but has its own limitations and the search for improved materials has led to an interest in hydrogels [29-31].

Hydrogel-based materials have been considered in a number of instances as wound dressings for second degree burns. When the skin is damaged, its ability to control evaporative water loss is impaired. Water transport properties (absorption, diffusion and evaporation) are vitally important such that the hydrogel must be able to control these properties. The hydrogel must be impermeable to bacteria that may cause infection but should be permeable to oxygen and water. Because of their hydrophilicity and biocompatibility, hydrogels have been of great interest to biomaterial scientists with both natural and synthetic hydrogels being targetted for use as wound dressings for second degree burns.

The main functions of a hydrogel in its use as a wound dressing are represented in Figure 2.1 and its main property requirements summarized in Table

2.1. Basically, it has to act as a temporary skin substitute to protect the wound while the healing process takes place.

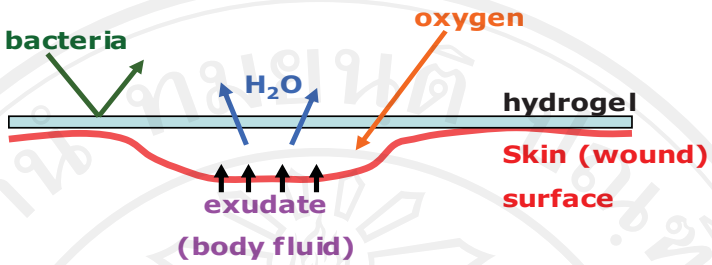



**Figure 2.1 :** The main functions of a hydrogel for use as a wound dressing.

**Table 2.1 :** Ideal properties of a wound dressing for second degree burns [32].

| Medical | Safety | General | Economic |
|---|---|---|---|
| 1.Good adhesion to the wound bed | 1.Sterility | 1.Oxygen permeability | 1.Availability |
| 2.Maintenance of moist environment | 2.Non-pyrogenicity | 2.Water vapour permeability | 2.Reasonable shelf-life |
| 3. Occlusiveness to microorganisms | 3.Non-toxicity | 3.Flexibility | 3. Cost effectiveness |
| 4. Control of water vapour loss | 4.Non-antigenicity | 4.Transparency | 4. Minimal storage requirements |
| 5. Absorption of wound exudate | 5.Lack of release of materials or particles that could interfere with the healing process | 5.Good handling characteristics | |
| 6. Conductive to cell proliferation | | | |
| 7.Antisepticity or compatibility with an antiseptic agent | | | |
| 8. Ability to improve the healing process and control pain | | | |
| 9. Durability | | | |
| 10. Ease of application and removal | | | |

The conceptualization and initial development of synthetic, polymeric hydrogels designed specifically for biomedical applications has generally been attributed to Wichterle and Lim [23]. In their article published in 1960, they described the use of poly(2-hydroxyethyl methacrylate), P(HEMA), crosslinked gels for a variety of medical applications and the rationale for their development. Since that seminal publication, a large body of literature on hydrogels for medical and other applications has developed. In 1962, Winter [33] discovered that a wound that was kept moist under an occlusive dressing healed faster than one which was allowed to dry out and develop a scab. Moist wound healing has been proven to be a faster, less painful method of healing with less scarring. In an extensive review on hydrogels published in 1976 [34], a number of questions and problems concerning hydrogel systems were raised.

The development of synthetic wound dressings used for the treatment of burns is currently a subject of great commercial interest. Although work on synthetic wound dressings has been in progress now for many years, the last two decades especially have seen significant movements in the field. Before examining the range of hydrogels in this area, it is appropriate to note the properties that a successful wound dressing material should possess. Stated simply, the material should be flexible, have sufficient tear strength and be non-antigenic and permeable to water vapour and metabolites whilst securely covering the wound to prevent bacterial infection. Hydrogels possess many of these properties and because of this they have been used extensively as wound dressing materials, sometimes alone but frequently in the form of composites principally to enhance their mechanical strength [35].



Research and development in the field of wound dressings has resulted in the fabrication and production of a wide variety of synthetic and biological dressings. Synthetic dressings based on polymeric sheets are now available as Tegaderm, Dermafilm, Opsite and Praflex, to name but a few. However, these are only suitable for superficial wounds, not for deeper wounds. Synthetic dressings made of polymer foams and sprays are also available commercially, as are composite dressings composed of two or more layers of polymers. In composite materials, the outer layer

is designed for durability and the inner layer for maximum adherence, elasticity and exudate absorption. Despite these advances and the wide range of commercial materials that now exists, the search continues for wound dressings with superior properties and functions [35].

## 2.2 Definitions of Hydrogels

Hydrogels, or water-containing gels, consist of polymeric networks characterized by hydrophilicity and insolubility in water. In water, they swell to an equilibrium volume but preserve their overall shape. The hydrophilicity is due to the presence of water-solubilising groups such as –OH, –COOH, $–CONH_2$, –CONH and $–SO_3H$. The insolubility and stability of shape are due to the presence of a three-dimensional network. The swollen state results from a balance between the dispersing forces acting on hydrated chains and cohesive forces that try to prevent the penetration of water into the network. Cohesive forces are most often due to covalent crosslinking; others are electrostatic, hydrophobic, or dipole-dipole in character [36]. The degree and nature of the crosslinking are responsible for many of the hydrogel's characteristic properties in the swollen state. The ability to imbibe water and ions without loss of shape or mechanical strength is a vitally important property in many natural hydrogels, such as those found in muscles, tendons and cartilage.

Alternatively, hydrogels have been defined as water-swollen hydrophilic materials which have the following properties in common [37]:

(a) They consist of polymeric chains that are crosslinked together either covalently or non-covalently.
(b) They are insoluble in water at physiologic temperature, pH and ionic strength.
(c) They will swell in water to an equilibrium water content of between 10% and 99% by weight at physiologic temperature, pH and ionic strength.

## 2.3 Classification of Hydrogels

Hydrogels can be classified in a number of ways according to their chemical and physical structure as well as their method of preparation, as shown in Table 2.2.

**Table 2.2** : Classification of hydrogels [38].

| Basis of Classification | Classes of Hydrogels | Description |
|---|---|---|
| Preparation | Homopolymer | One type of hydrophilic monomer |
| | Copolymer | Two types of monomer; one must be hydrophilic |
| | Multi-polymer | Three or more monomers; one must be hydrophilic |
| | Interpenetrating network (IPN) | One crosslinked polymer is swollen in a second monomer that is reacted to form a second intermeshing network |
| Ionic charge | Neutral | No charge |
| | Anionic | Negatively charged |
| | Cationic | Positively charged |
| | Ampholytic | Capable of behaving both positively and negatively |
| Physical and structural features | Amorphous | Randomly ordered polymer chains |
| | Semi-crystalline | Contains dense regions of ordered polymer chains (crystallites) |
| | Hydrogen-bonded | 3-dimensional network held together by hydrogen bonds |

## 2.4 Water in Hydrogels

### 2.4.1 The Hydrogel-Water Interface [39]

The hydrogel interface with water presents a unique and complex situation. A vertical surface gradient probably exists ranging from bulk hydrated polymer, through diffuse polymer chains, and finally to bulk water (Figures 2.2 and 2.3). Throughout this interfacial region are varying amounts of free water and bound water, as well as less tightly bound oriented (or structured) water. Attempts have been made to measure the relative proportions of each of these types of water in bulk hydrogels. However, such measurements at the interfacial region have not been attempted. Since interactions with proteins, blood, and tissue will be localized at this interface, understanding its nature is critical to the use of hydrogels in biomedical applications.

Some of the techniques that have been used to study the hydrogel-water interface include hydrodynamic flow studies and contact angle measurements. These studies have indicated that the hydrogel interface is different in surface character in air (dehydrated) and in water, that the interfacial tension of the interface in water approaches zero, and that the surface is microscopically deformable under flow.

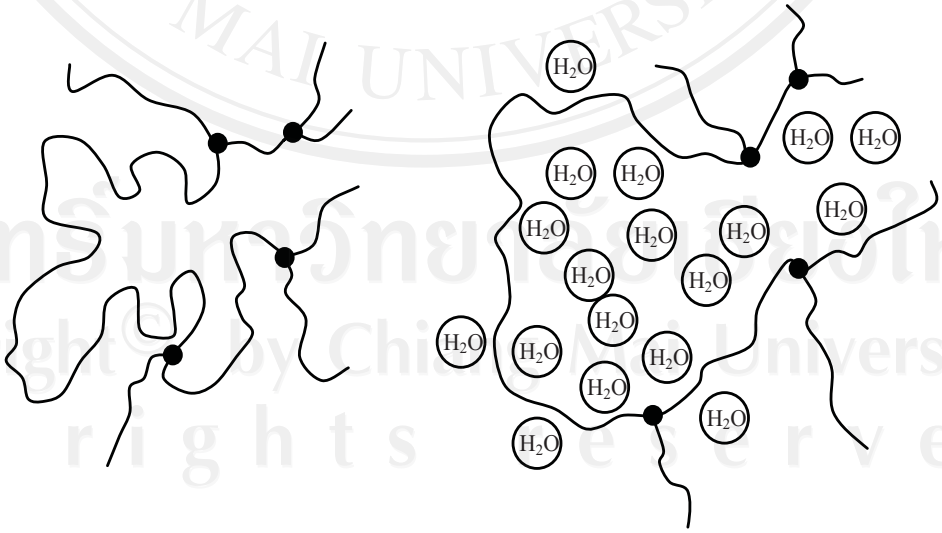



**Figure 2.2 :** Schematic representation of a polymer chain expanded by water absorption in a hydrogel [39].

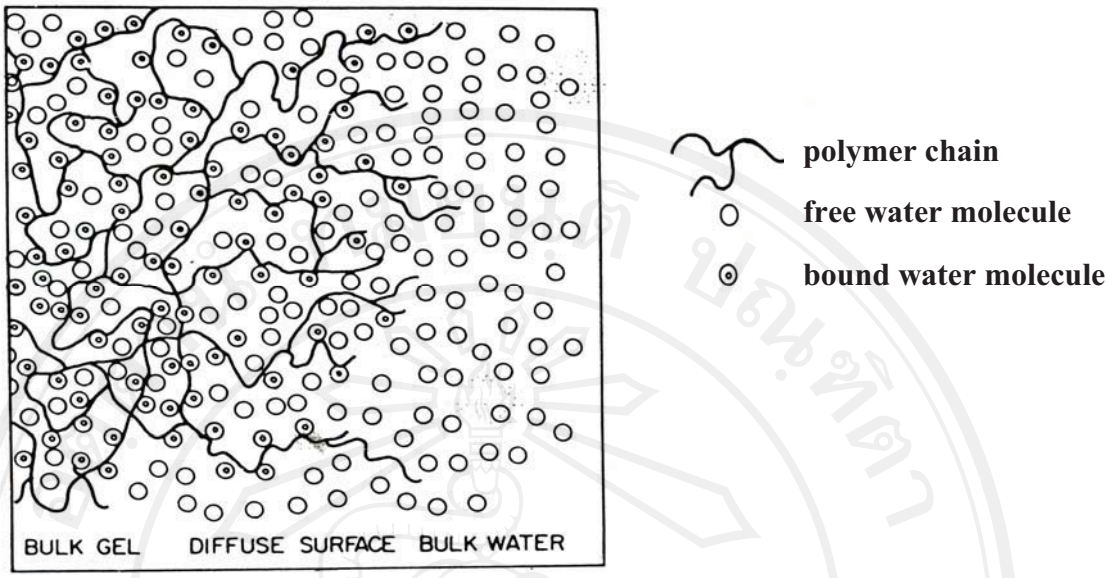



**Figure 2.3 :** Schematic representation of the hydrogel-water interface [39]. (Regions of structured water might be expected in the vicinity of the bound water molecules due their strong, fixed dipoles.)

### 2.4.2 Equilibrium Water Content

The ***equilibrium water content*** (EWC) of a hydrogel is its single most important property as it is this water that gives hydrogels the unique properties that favour their use as biomaterials. The water held by the polymer affects the biocompatibility, mechanical properties and surface properties of the gel, acting as a transport medium for dissolved oxygen and protein/peptide molecules found in the extracellular fluid, a plasticizer, and a "bridge" between the different surface energies of the polymer and body fluids. Since the water present in the hydrogel affects the density and refractive index of the polymer, measurement of these properties may also be used to determine the EWC [40].

The EWC of a hydrogel is determined by internal factors such as the nature and quantity of the constituent hydrophilic monomer and the nature and density of any crosslinking agent(s). Whilst the hydrophilic network is osmotically driven

towards infinite dilution, the covalent crosslinks between the polymer chains oppose such a degree of swelling, creating an elastic network retraction force. Together these dictate an equilibrium swelling point of the hydrogel [41].

According to the well-known Flory-Rehner theory [42], when a solvent is added to a crosslinked polymer, it tries to dissolve the polymer and so enters into the crosslinked network and solubilizes the polymer chains. However, the crosslinks prevent the chains from separating completely and moving away from each other, as they would do in a true solution. Thus, the solution forces pull the chains apart, stretching them between the crosslinks. This produces a swelling of the polymer which only ceases when the elastic restoring force created in the stretched chains exactly balances the solution driving force, as shown in Figure 2.4 below.

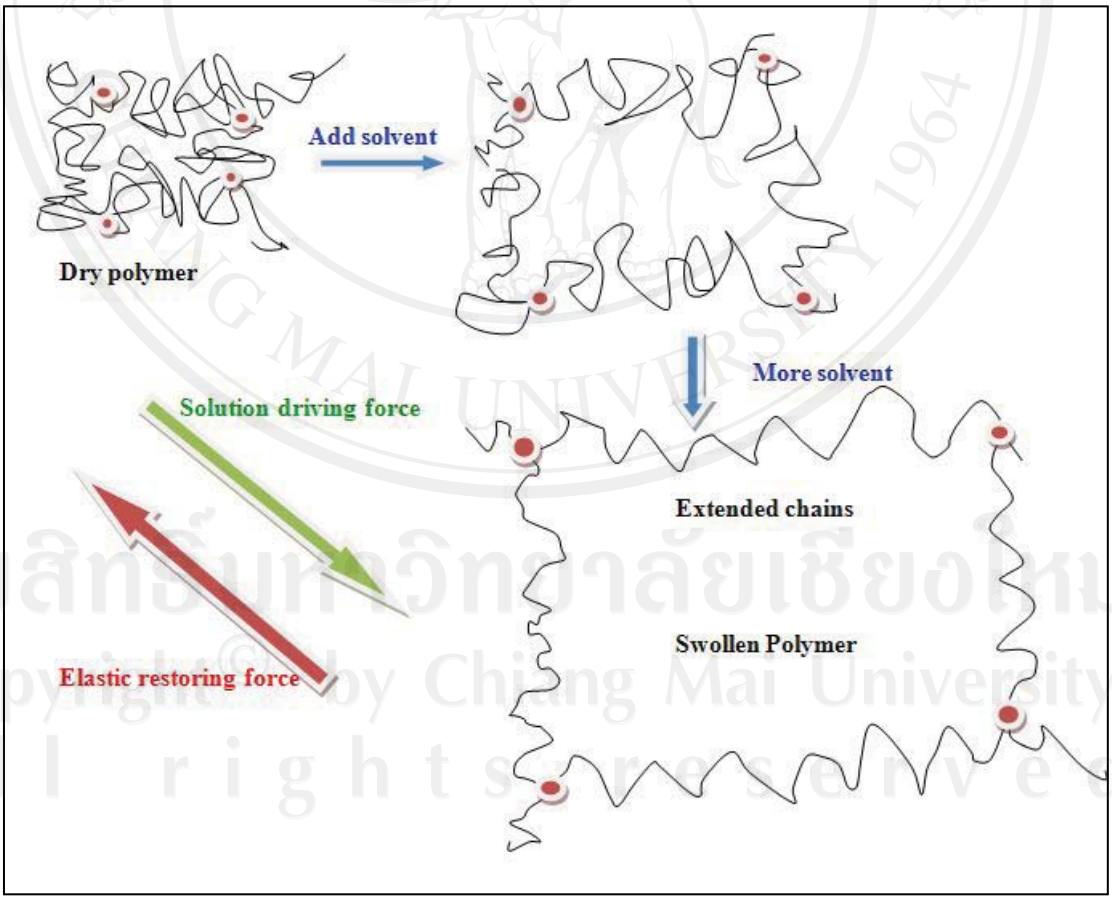



**Figure 2.4** : Schematic representation of the equilibrium swelling of a crosslinked polymer by a solvent

The Flory-Rehner theory describes the thermodynamics of this balance between the solution driving force and the elastic restoring force. The entropy change caused by mixing the polymer and the solvent is positive and favours swelling. For a strong polymer-solvent interaction, the enthalpy change may be negative but, even when slightly positive, is less important than the entropy increase. This is the normal thermodynamic treatment of dissolving a polymer in a good solvent.

In contrast, the entropy change caused by the reduction in the number of possible chain conformations as the polymer network swells and the chains between the crosslink points are stretched is negative and opposes swelling. This is the normal entropic restoring force of rubber elasticity. Thus, the amount of swelling is determined by the balance of the solution driving force against the elastic restoring force. A higher polymer-solvent interaction leads to a higher solution driving force and so to more swelling. A low molecular weight between crosslinks leads to a higher restoring force and so to less swelling. This Flory-Rehner equilibrium swelling theory takes the solubility terms given by the Flory-Huggins theory and adds the stretching terms as given first by Guth and then used by Mooney and Rivlin, leading to the Flory-Rehner Equation:

$$-[\ln(1 - \nu_2) + \nu_2 + \chi_1 \nu_2^2] = (V_1/M_c) [\nu_2^{1/3} - \nu_2/2]$$

where

$\chi_1$ = the Flory polymer-solvent interaction term (as in the Flory-Huggins Equation)

$\nu_2$ = the volume fraction of the polymer in the swollen mass

$V_1$ = the molar volume of the solvent

$M_c$ = the average molecular weight of chain segments between crosslinks (as in the Mooney-Rivlin Equation)

Returning now to the equilibrium swelling of hydrogels, the EWC is further affected by external environmental factors such as temperature, pH and the tonicity of the hydrating medium [43]. The effects of temperature on the EWC and therefore on the dimensions of hydrogels are important when considering their use in biomedical applications. Variations in the size and water content of hydrogels, at temperatures ranging from room temperature to body temperature to the higher temperatures necessary in sterilization of the gels prior to their use, and the consequences for their suitability for specific applications must be considered. Any increase in temperature leads to a decrease in what is sometimes referred to as "hydrophobic hydration" and an increased formation of hydrophobic bonds. These hydrophobic bonds are weak van der Waals interactions between non-polar groups which act as physical crosslinks within the polymer matrix, thereby reducing the free volume and hence the EWC of the hydrogel. However, hydrophilic hydration, the formation of hydrogen bonds between polar groups of the polymer and water in the hydrating medium, increases with increasing temperature. As a result, the polymer network expands entropically leading to an increased capacity for the hydrogel to absorb water [40].

### 2.4.3 Volume Fraction of Water Within Hydrogels

Many hydrogels become adhesive when hydrated and their degree of adhesivity is affected by the volume fraction of water within the gel. The partial hydration of the gel and its associated swell allows a greater degree of rotation of the polymer chains whilst maintaining the gel's high residual capacity for water uptake. As a result, partially hydrated, high EWC hydrogels are particularly adhesive to moist soft tissue. This property is exploited in a number of biomedical applications of hydrogels such as wound dressings and electrodes. Control of both the EWC and degree of hydration of a hydrogel can be used to modify the physical properties and adhesive behaviour of the hydrogel under specific conditions.

### 2.4.4 Water-Structuring Within Hydrogels

Independent of the EWC, water structuring within a hydrogel is also an important influence on its properties. Though there is still some dispute concerning the nature and number of states of water within hydrogels, it is now widely accepted that the water exists in a continuum between two extreme states of "bound" and "free" water. When a hydrogel is first hydrated, the water primarily binds to the most polar, hydrophilic groups. Consequent swelling of the polymer network exposes hydrophobic groups that bind hydrophobically with the water. These primary and secondary bound water states are grouped together as total bound water. Osmotically driven water that subsequently swells the gel, filling the spaces between the crosslinked network chains, is known as free water [41]. The elastic network retraction force which limits this swelling is controlled by the crosslinks within the polymer network. As crosslink density increases, increased steric occlusion of hydrophilic binding sites and decreased mobility within the polymer network greatly reduces the free water content. The ratio of bound and free water is thought to play a central role in determining the surface, transport, and mechanical properties of hydrogels.

### 2.4.5 Effects of Crosslink Density

Hydrogels derive most of their mechanical strength from crosslinks, both chemical and physical, within the material that form a 3-dimensional network of the polymer chains. By using higher concentrations of crosslinking agent in hydrogel synthesis, crosslink density can be increased, dramatically increasing the mechanical strength of the gel. It is important to consider, however, that this is likely to be accompanied by other less desirable changes to other properties of the material. Diffusion within the gel will be impeded by additional crosslinks, resulting in reduced swell and release rates, and the EWC of the hydrogel will be lowered due to an increased elastic network retraction force. At a crosslink density specific to a particular hydrogel composition, these effects will be such that the material

synthesised no longer behaves as a “gel”, instead possessing the properties of a glassy plastic [40].

## 2.5 Fundamentals of Transmission [44]

The transmission or movement of molecules inside polymers is coordinated with, or controlled by, chain movements in the polymer matrix. Such phenomena are important in a wide variety of uses ranging from packaging, through membrane separation processes, to controlled drug release.

When discussing molecular transmission, it is important to distinguish between *permeability,* P, and *diffusivity,* D. The former is a measure of the amount of material that can be absorbed into one side of a polymer sample and then extracted from the other side. This penetration of a small molecular species into a bulk polymer is called *permeation*. On the other hand, the statistical random walk of sorbate molecules inside the polymer is called *diffusion.* Another important term is *solubility,* S. Whilst the ability for a molecule to move through the matrix is clearly important, its solubility can also be a significant factor in defining the permeability. In fact, the permeability is directly related to the product of the diffusivity and the solubility:

$$P = D \times S$$

The movement of small molecules into and through a polymer depends significantly on two phenomena. The first is the nature of the interactions between the diffusing molecule and the polymer chain, as evidenced macroscopically in the solubility (or miscibility) of the two. The second is the availability of free volume into which the diffusing species can move. For this reason, diffusivities differ markedly between different polymer types and also between the crystal, glass and rubber forms. A useful rule of thumb is that the lower the available free volume, the slower is the diffusion but the greater is the selectivity of the transport process.

Permeability measures both the amount of sorbate molecules in the polymer and the speed with which they can move. The effect of temperature is incorporated into a composite "permeation activation energy" which is the sum of the enthalpy of solution and the activation energy for diffusion. Because molecules of like chemical structures are usually more miscible than dissimilar ones, another good rule of thumb is that the permeation of molecules in a polymer is highest when the two are chemically similar.

### 2.5.1 Permeation of Permanent Gases

In amorphous or rubbery polymers, a permanent gas forms only a very dilute solution in the polymer. Consequently, there is no distortion of the polymer matrix by the gas and the diffusion coefficient is independent of the amount of absorbed gas. In this case, the permeation follows the ideal product of solubility and diffusivity rather closely. If the temperature dependence of permeability is given by the exponential Arrhenius-type equation, then

$$P = P_0 \exp(-\Delta E_p/RT)$$

and

$$\Delta E_p = \Delta H_s + \Delta E_D$$

where

$\Delta E_p$ = activation energy for permeation
$\Delta H_s$ = enthalpy of solution
and $\Delta E_D$ = activation energy for diffusion

In a homogeneous substrate, the diffusivity and permeability are isotropic. However, the polymer may have been oriented during processing. If that is the case, permeation is greater along the orientation dimension than perpendicular to it. It has also been found that polymers with bulky groups on the backbone or in the side chain have lower permeabilities than sterically less hindered materials.

### 2.5.2 Permeation of Condensable Vapours

Permeation of vapours which are condensable or which interact strongly with groups on the polymer chain does not follow the simple treatment outlined previously. There are two important reasons for this.

Firstly, the presence of sorbate affects the chain segment jump process. Thus, the diffusion coefficient is not independent of the concentration of diffusing species. Secondly, as the temperature is raised, the diffusion coefficient increases but the solubility, if it follows Henry's Law, decreases. Then, at temperatures above the polymer's glass transition temperature, these two factors balance each other out and the permeation does not increase as much as might be expected.

Generally, there are two types of permeation. Above the polymer's glass transition temperature, the rate of segmental relaxation is greater than the rate of sorbate penetration such that the permeability is little affected by sorbate-induced swelling. Hence, the diffusivity is not very concentration-dependent. This is the situation with many hydrocarbon sorbates in commercial rubbers. On the other hand, below the glass transition temperature, the segmental relaxation rate is much less than the diffusivity so that the permeability is very dependent on swelling factors.

Of particular technological importance is the permeation of water. Here the ability of the water molecule to form hydrogen bonds either with groups in the polymer or with other water molecules has an enormous effect. In the former case, in hydrophilic polymers, the water exerts a swelling, plasticizing effect. The diffusivity increases with penetrant concentration. However, in hydrophobic polymers, the water tends to bond to itself forming clusters of water molecules. This decreases the amount of water diffusing through the polymer and so the diffusivity decreases with overall concentration. Combining these two effects, it is possible to synthesize polymer films which have controlled barrier-permeation properties.

### 2.5.3 Technological Applications

**Medical Uses**: The control of water transmission through a polymer film or sheet is vitally important in wound dressings. The material covering the wound must permit a controlled transit of water but must provide a barrier against bacterial and other infections. This is achieved by the use of partially swollen hydrogels formed from crosslinked hydrophilic polymers. The small water molecules have a high diffusivity, while the relatively large microorganisms cannot penetrate the film. Indeed, antibiotic substances can be incorporated into the film, further aiding its protective properties.

**Membrane Separations**: Although medical uses are exciting, the largest tonnages are for membrane separation and packaging processes. Semi-permeable membranes have been used over many years for the purification of sea water by reverse osmosis. A hydrophilic polymer membrane allows the passage of small water molecules but not the sodium and chloride ions surrounded by their hydration shells. Then, application of pressure to the brine side overcomes the osmotic pressure of the solution, forcing water through the membrane into the low pressure purified side. The pore size for this permeation is controlled by the extent of swelling and crosslinking in the polymer. Modified cellulose acetate membranes swollen with 20% to 30% by volume of water are widely used. At the same time, the membrane must support the pressure difference, which the swollen separation film cannot. This is achieved by supporting the permeation film on an open, strong network of some hydrophobic polymer. However, two general aspects are important here. The first is the nature of the intermolecular interactions between the polymer and potential sorbates. Thus, hydrophilic polymers are used to permit the passage of water and polar substances while restricting the permeation of non-polar materials. Conversely, hydrophobic polymers have the opposite effect. The second is the balance between crosslinking and swelling in determining the “pore size” of the membrane so that selectivity can be based on the molecular volume of the sorbate.

## 2.6 Synthesis of Hydrogels

Hydrogels are produced by the polymerisation of hydrophilic monomers in the presence of small concentrations of initiator with small concentrations of multifunctional crosslinking agents to produce hydrophilic networks of crosslinked polymer chains. A wide variety of materials can be used to prepare hydrogels including materials of natural origin (e.g., proteins such as collagen, polysaccharides such as chitosan or hyaluronic acid) which may or may not require structural modification. However, nowadays the vast majority of hydrogels used in biomedical applications are based on synthetic polymers which can be structurally designed more easily to give properties tailored to meet the requirements of specific applications. Some of the more commonly used monomers for hydrogel synthesis are shown in Figure 2.5 below.

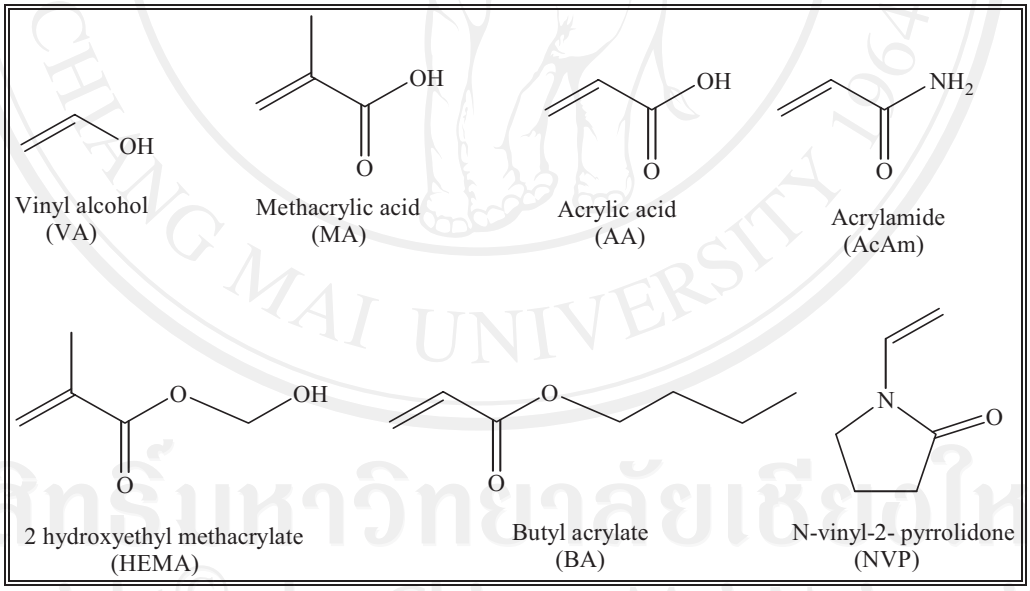



**Figure 2.5** : Various monomers commonly used in the synthesis of hydrogels.

Since the monomers in Figure 2.5 are all vinyl-type monomers, synthesis is usually carried out via addition polymerisation using thermal, redox or photoinitiation.

## 2.7 Hydrogels in the Wound Care Market [45]

Recent worldwide industry reports estimated that the wound care market wound exceed US 11.8 billion by 2009 with yearly growth for all products (devices for wound closure such as sutures and staples, dressings, adhesives, etc.) projected to be in excess of 7%. European markets have accounted for about half of the total spending. A list of just some of the many hydrogel sheet wound care products currently available in the commercial market is given in Table 2.3.

**Table 2.3 :** Commercial hydrogel wound care products currently available in the market [45].

| **Products** | **Manufacturers** |
|---|---|
| Tegagel | 3M |
| Vigilon | Bard |
| ClearSite | Conmed Corporation |
| AQUASORB | DeRoyal |
| FLEXDERM | Bertek (Dow Hickam) |
| NU-GEL | Johnson & Johnson |
| CURAGEL | Kendall |
| Derma-Gel | Medline Industries |
| FlexiGel | Smith & Nephew |

## 2.8 Aims and Context of this Research

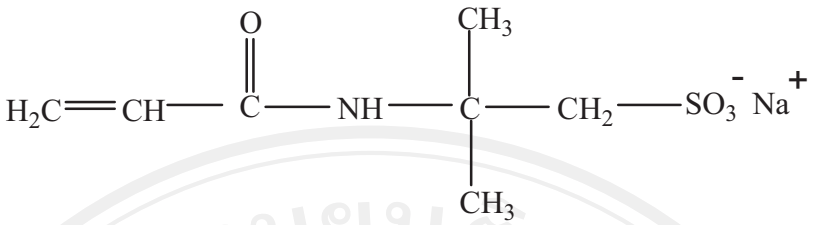
At present, Thailand continues to import biomedical hydrogel products, including wound dressings, at great expense. This present research work in its wider context is therefore aimed at developing a capability to manufacture these products in Thailand with the initial emphasis on wound dressings for second degree burns.

From a commercial point of view, the immediate need is not only for an effective wound dressing but also for an affordable one. In other words, the product price should not exaggerate expenses incurred by the hospital stay and related medical care. In recent years, hydrogels derived from poly(2-acrylamido-2-methylpropane sulfonic acid), poly(AMPS), and its sodium salt, poly(Na-AMPS) have attracted considerable attention for use in biomedical applications with poly(Na-AMPS) generally preferred for wound care.

The main objective of this thesis is to develop a hydrogel sheet for use as a wound dressing which need not be changed every day. This involves:

1. Synthesis of poly(Na-AMPS) hydrogels in thin sheet form
2. Effects of various synthesis, structural and compositional variables
3. Property testing of the hydrogel sheets

In previous work, the Biomedical Polymers Technology Unit at Chiang Mai University has studied synthetic hydrogels based on 2-hydroxyethyl methacrylate (HEMA) and also chitosan for use as wound dressings [46]. However, these hydrogels still had shortcomings associated with their preparation, fabrication and overall balance of properties. Thus, attention in this work has turned to Na-AMPS as a water-soluble monomer which can be polymerised in aqueous solution. Consequently, the hydrogel is formed in a matrix-expanded hydrated state which has the added advantage of reducing the amount of unwanted traces of residual monomer.



**sodium 2-acrylamido-2-methylpropane sulfonate (Na-AMPS)**

There are currently many papers and patents citing the use of AMPS and Na-AMPS monomers [47-55]. Rosso and co-workers [47] studied new polyelectrolyte hydrogels for biomedical applications synthesized from AMPS and its copolymers. Their studies showed that cationic copolymers have good cell adhesion, whereas anionic copolymers have poor cell adhesion. Jadranka and Allan reported the free radical copolymerisation of AMPS and acrylamide by thermal initiation [48]. Similarly, Yang and co-workers described the synthesis and properties of copolymers of both AMPS and Na-AMPS with acrylamide, also by thermal initiation [49]. In contrast, Durmaz and Okey described the synthesis of AMPS-acrylamide hydrogels by redox initiation [50]. Abdel-Azim and co-workers studied the synthesis of polymeric hydrogels containing the sulfonate group and discussed the effect of crosslinking on the swelling properties [51]. Recently, photoinitiation has been reported in many papers [52-55], although not for AMPS or Na-AMPS.

In the light of this previous work, this research thesis now aims to contribute to the current state of knowledge by comparing the different methods of initiation as well as different initiator-crosslinker systems on the properties of poly(Na-AMPS) hydrogels polymerised in aqueous solution. In addition, property modification through humectant addition and copolymerisation will also be briefly studied as extensions of the main study.