CHAPTER 2

BIOMEDICAL APPLICATIONS OF SYNTHETIC HYDROGELS

2.1 Introduction [13,14]

The term ***hydrogel*** refers to a broad class of polymeric materials which swell extensively, but do not dissolve in water. They include many natural materials of both plant and animal origin. Because of the similarity between synthetic and natural hydrogels, these gels have been used in a wide variety of biomedical applications, and the number is growing. Presently, these applications include wound dressings, suture coatings, contact lenses and artificial organs. Since biocompatibility apparently depends on water content, characterisation of the amount of imbibed water in the swollen gel is essential.

The conceptualisation and initial development of synthetic polymeric hydrogels for biomedical applications was accomplished by Wichterle and Lim [13] who described the potential use of crosslinked poly(2-hydroxyethyl methacrylate), P(HEMA), gels as biomaterials in a 1960 article. Although the linear polymer was first prepared as early as 1936 by Du Pont scientists, they did not polymerise the monomer in the presence of a crosslinking agent in an aqueous medium as Wichterle and Lim did in 1960. Since then, P(HEMA) has become the most widely used and studied synthetic hydrogel for a variety of biomedical applications. In an extensive review on hydrogels published in 1976, a number of questions and problems concerning hydrogel systems were raised [14].

2.2 Definitions of Hydrogels [15,16]

Hydrogels, or water-containing gels, consist of polymeric networks characterised by hydrophilicity and insolubility in water. In water, they swell to an equilibrium volume but preserve their shape. The hydrophilicity is due to the presence of water-solubilizing groups, such as -OH, -COOH, $-CONH_2$, -CONH-, $-SO_3H$, etc. 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 do not 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 [17]. The degree and nature of crosslinking and the tacticity and crystallinity of the polymer are responsible for its characteristics in the swollen state. The ability to imbibe water and ions without the loss of shape or mechanical strength is valuable 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 [18]:

(a) They consist of polymeric chains that are crosslinked together either covalently or non-covalently.

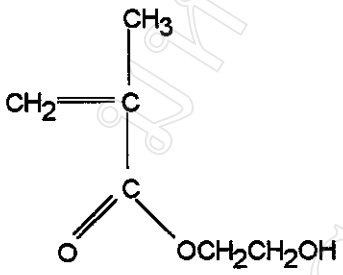
(b) They are insoluble in water at physiologic temperature, pH and ionic strength.

(c) They will swell in water to an equilibrium value of 10% to 98% H_2O at physiologic temperature, pH and ionic strength. The water content (% H_2O) is defined as :

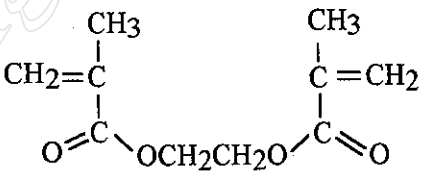
$$\% H_2O = \frac{\text{(weight of swollen polymer) - (weight of dry polymer)}}{\text{weight of swollen polymer}} \times 100 \qquad (1)$$

2.3 Hydrogels Based on Hydroxyalkyl Methacrylates [15]

The most widely used hydrogel in this class of synthetic polymer is poly(2-hydroxyethyl methacrylate, (PHEMA). It is highly stable to hydrolysis because of the configuration of the ester bond. The properties of P(HEMA) can be modified by crosslinking, but its maximum swelling in water is thermodynamically limited [19] to about 40%, with a very low network density and poor mechanical strength [20]. Refojo and Yasuda [21] have described the synthesis of P(HEMA) by several methods, mainly involving bulk polymerisation of the HEMA monomer followed by crosslinking with a suitable crosslinking agent such as ethylene glycol dimethacrylate (EGDMA).



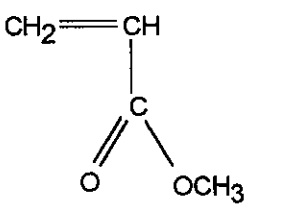
2-hydroxyethyl methacrylate (HEMA)



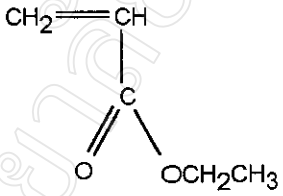
ethylene glycol dimethacrylate (EGDMA)

In order to improve its mechanical properties, HEMA is often copolymerised with hydrophobic comonomers to obtain hydrogels with superior machinability and

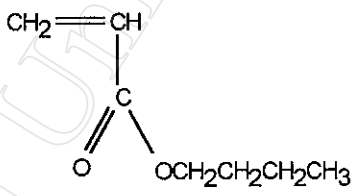
tensile strength [22]. Good machinability and elasticity in combination with good wettability, biocompatibility, and oxygen permeability are desired properties in biomaterials, especially in surgery. Comonomers that enhance hydrophobic interactions between chains are used to improve hydrogels for use in contact lenses and surgical implants. For example, butyl acrylate (BA) and / or ethyl acrylate (EA) added to HEMA increase the tensile strength of the hydrogel [23]. However, excessively long hydrophobic side chains are unsuitable for swelling gels. Methyl acrylate (MA) with HEMA gives a copolymer that is soft and pliable even in the dry state.



methyl acrylate (MA)



ethyl acrylate (EA)



butyl acrylate (BA)

2.4 The Hydrogel - Water Interface [14]

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 (Figure 2.1). 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.

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) or in water, that the interfacial tension of the interface in water approaches zero, and that the surface is microscopically deformable under flow.

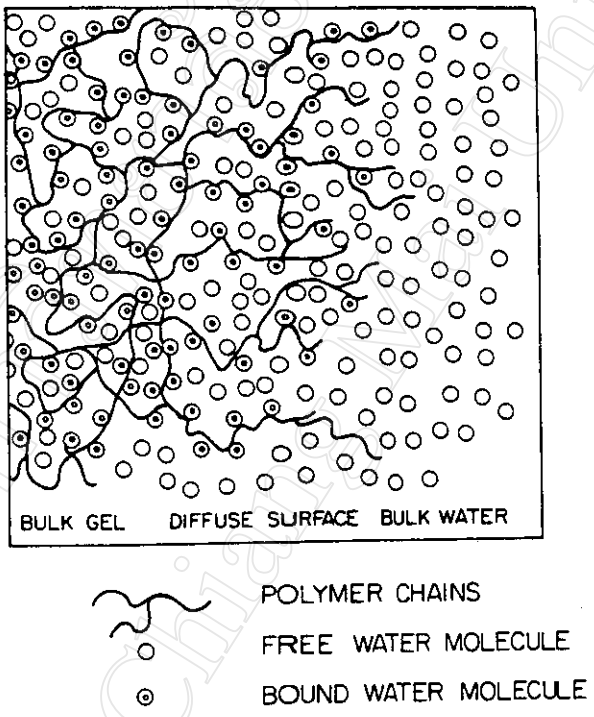


Figure 2.1 : Schematic representation of the hydrogel-water interface [14]. (Structured water is not shown in this diagram. Regions of structured water might be expected in the vicinity of the bound water molecules due to their strong, fixed dipoles.)

2.5 Factors Affecting the Swelling of Hydrogels [13,14]

There are several factors, favorable and inhibitive, which influence the degree of hydrogel swelling. Some of the favorable influences on swelling are osmotic potential, strong interactions with water, high free volume, high chain flexibility and low crosslink density. Conversely, the inhibitive factors affecting swelling are weak interactions with water, low free volume, low chain flexibility, and high crosslink density. Thus, strong positive interactions between chemical groups on the polymer chain and water, such as hydrogen bonding, increase the driving force for swelling. Some of these factors are summarized in Table 2.1.

Table 2.1 : Factors that influence the swelling of hydrogels [18].

Favorable to Swelling	Inhibit Swelling
Osmotic potential	Weak interactions with H_2O
Strong interactions with H_2O	Low free volume
High free volume	Low chain flexibility
High chain flexibility	High crosslink density
Low crosslink density	

If a slab of dehydrated polymer is placed in water, there will be an osmotic driving force for the water to enter the water-free region within the polymer. As water enters the polymer, the chains extend and exert a resistive force because swelling places the chains into less entropically desired configurations. This is illustrated schematically in Figure 2.2. Figure 2.2 (a) represents the most entropically favorable

configuration, given the mechanical constraints of the polymer chain. The entrance of water into the system will necessitate its expansion and a consequent ordering of the polymer chain (Figure 2.2 (b)). Since the chains will be elongated into less entropically desirable configurations, they exert a resistive force. When this resistive force balances the osmotic force driving water into the polymer, at that point, the ***equilibrium degree of swelling*** will have been achieved.* Because a high crosslink density of the network (a shorter distance between crosslink points) or a stiffer polymer backbone intensifies the resistive force to chain extension, a more highly crosslinked system or a polymer with a stiffer backbone will swell less. Consequently, more highly crosslinked systems demonstrate lower degrees of equilibrium swelling. If the polymer chains are inflexible, swelling will also be inhibited due to increased resistance to deformation from their equilibrium configurations, Finally, if the free volume in the polymer is too low, water may be unable to penetrate the polymer matrix to initiate the swelling process. All of these structural factors influencing hydrogel swelling are controllable by the appropriate choice of monomer(s) and polymerisation conditions.

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* More rigorously, the thermodynamic activity of the solvent (H_2O) in the gel will change until it is equal to its activity in the pure solvent.

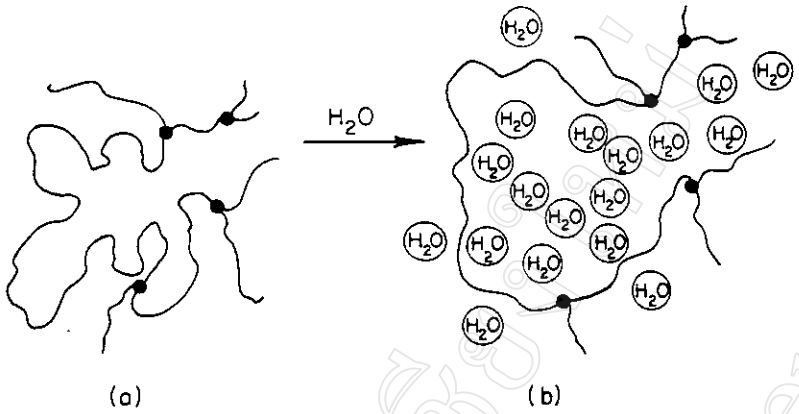


Figure 2.2 : Water entrance into a single, idealized hydrogel chain segment [14].

2.6 Synthesis and Fabrication of Hydrogels [13,18]

Many different polymeric structures can be classified as hydrogels. Table 2.2 lists some of the many monomers used in hydrogel syntheses. In Table 2.2, the type of monomers listed are divided into four categories; namely, neutral, acidic or anionic, basic or cationic, and crosslinker. Most of the monomers are hydrophilic and have strong positive interactions with water. Thus, the resulting hydrogels display high degrees of swelling.

One way of reducing the extent of swelling in water is by copolymerisation of a combination of hydrophilic and hydrophobic monomers. Also hydrogels are sometimes formed by conversion of an already existing polymer. Table 2.3 lists examples of polymers that can be converted into hydrogels.

Table 2.2 : Monomers used in hydrogel preparation [13].

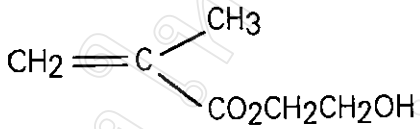
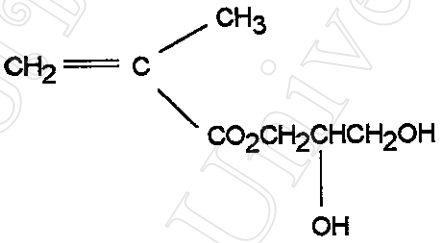
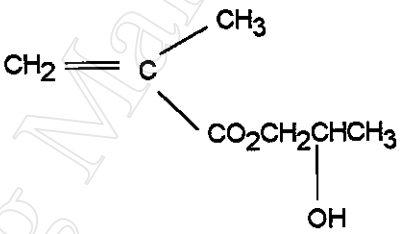
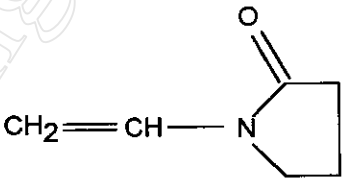
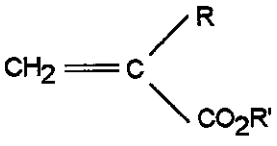
NAME	CHEMICAL STRUCTURE
<u>NEUTRAL</u>	
2-Hydroxyethyl methacrylate	
Glyceryl methacrylate	
Propylene glycol methacrylate	
N-vinyl pyrrolidone	
Acrylics	 (R = H, CH_3) (R' = CH_3, C_4H_9)

Table 2.2 : (continued)

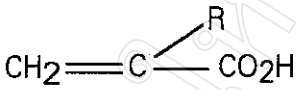
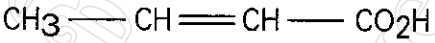
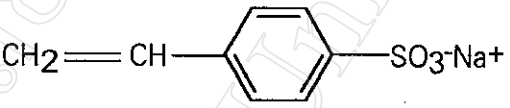
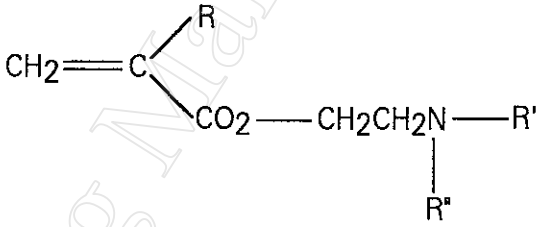
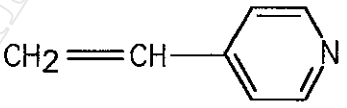
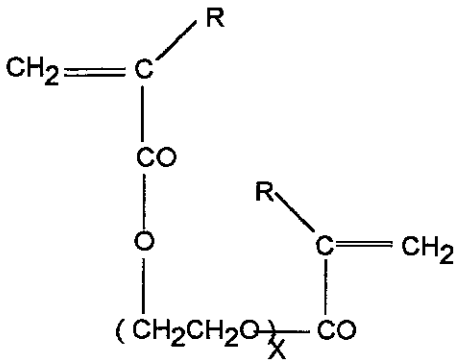
NAME	CHEMICAL STRUCTURE
ACIDIC or ANIONIC	
Acrylic acid, and its derivatives	 (R = H, CH_3)
Crotonic acid	
Sodium styrene sulfonate	
BASIC or CATIONIC	
Aminoethyl methacrylate, and its dervatives	 (R, R', R" = H, CH_3, C_4H_9)
4-Vinyl pyridine	
CROSSLINKERS	
Ethylene glycol dimethacrylate and its derivatives	 (R = CH_3)

Table 2.2 : (continued)

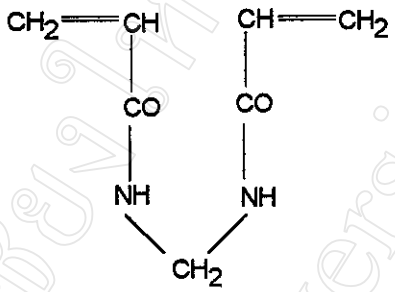
NAME	CHEMICAL STRUCTURE
Methylene - bis - acrylamide	

Table 2.3 : Converted polymers used as hydrogels [13].

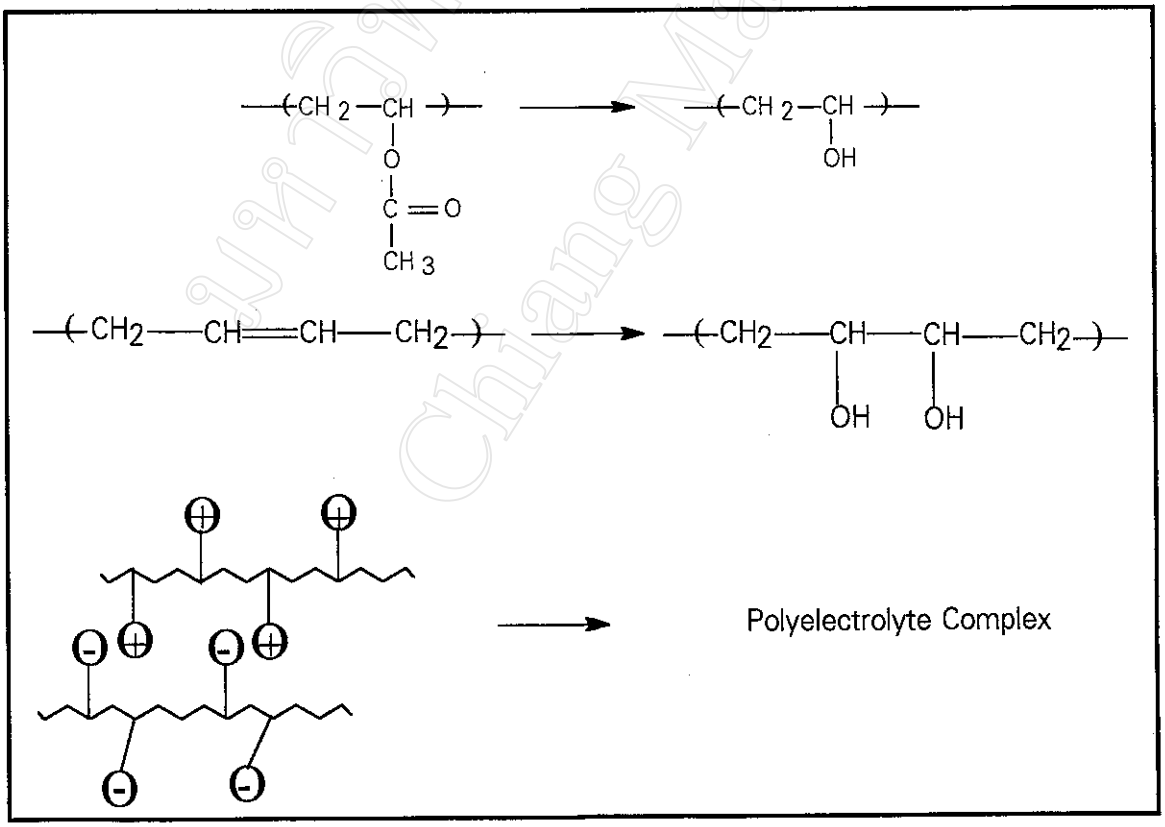
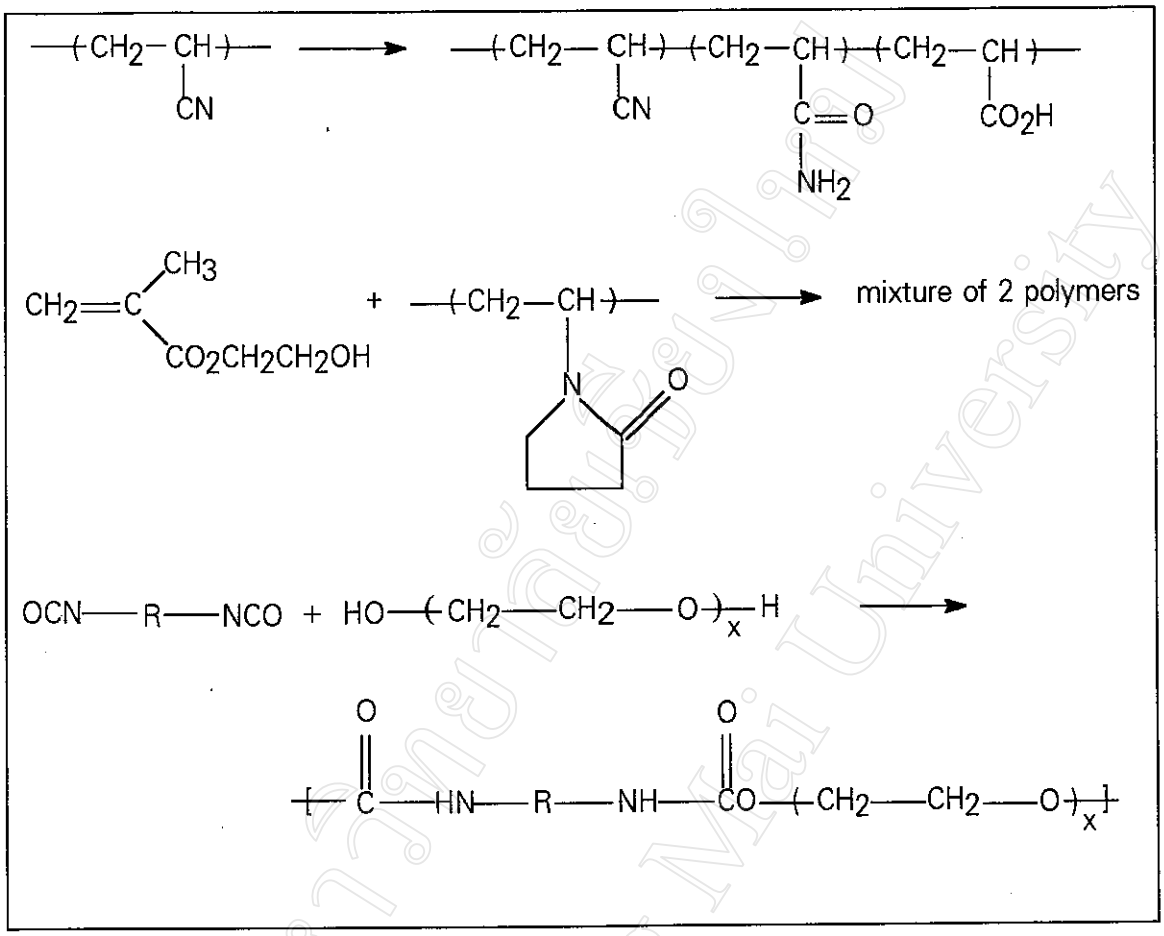


Table 2.3 : (continued)



Polymers fabricated from the structures listed in Tables 2.2 and 2.3 are insoluble in aqueous media after they have been made into hydrogels. The polymer chains are interconnected by covalent bonds. It is obvious from the quantity of listed monomers and convertible polymers that many different hydrogels with widely varying properties are possible. Hydrogels are fabricated into useful forms using a variety of techniques, where the specific approach depends on the polymer type. However, the objectives in all cases are the same : to prepare a hydrophilic polymer which maintains its integrity in water, which is in the precise geometric configuration for the

required application, and which has sufficient mechanical strength and appropriate compliance to make it useful for that application. Figure 2.3 displays schematically some of these fabrication methods.

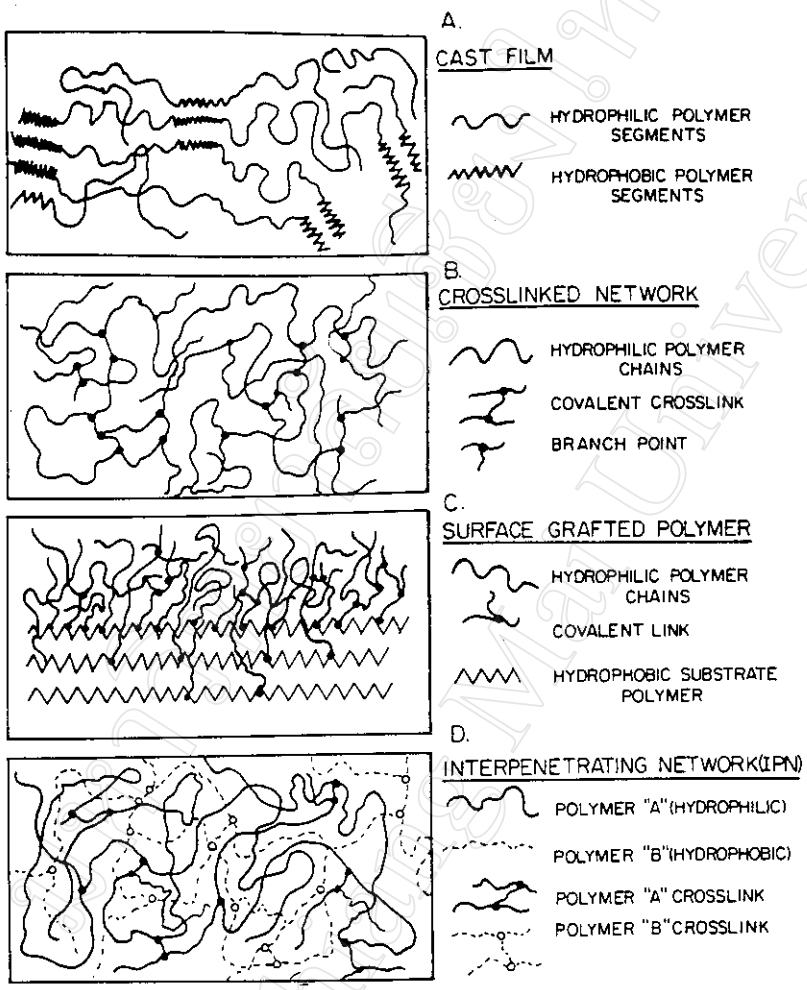


Figure 2.3 : Fabrication of hydrogels [24].

Cast films [Figure 2.3 (a)] are frequently used as coatings for other materials and usually require noncovalent forces (e.g., hydrophobic bonding) to prevent dissoluton of the polymer in aqueous media. Such films are either hydrophobically or covalently bonded to the material of interest. However, in many cases, films can be

covalently crosslinked after casting. An example of the use of this type of coating is the work of Tollar et al. [24]. Indeed, as early as 1969, Tollar and his colleagues used P(HEMA) hydrogel as a coating for surgical sutures with excellent results. Also, they successfully loaded the gel coating with antibiotics to facilitate wound healing. Figure 2.3(b) shows the preparation of the mould crosslinked hydrogel network. Such a network is formed by injecting a mixture of monomer, crosslinking agent and initiator into a mould. Sometimes a solvent is also added to the mixture as diluent to yield a more porous gel. Hydrogels prepared in this manner have been used in such applications as plastic surgery for breast augmentation, as artificial membranes in corneal surgery, and in otolaryngology for covering ear drum perforation and nasal pyramids [25]. Surface grafting [Figure 2.3(c)] of hydrogels to other polymers is a fabricating technique in which the hydrophilic polymer is made water-insoluble by bonding it to an insoluble substrate. The generally low mechanical strength of hydrogels can be improved by bonding to a mechanically strong polymer, while fabrication is simplified since only the substrate need be formed into a specific shape. Ratner and Hoffman [26] have discussed in detail techniques for preparing grafted hydrogels. Interpenetrating polymer networks (IPN) can be prepared by forming crosslinked hydrogel systems within other polymer networks [Figure 2.3(d)] where both are topologically independent but inseparable. Such systems are also used to mechanically strengthen hydrogels. Finally, hydrogels can be formed as uniform microspheres in sizes ranging from 0.3 mμ to 3.4 μm [27].

The synthesis and fabrication of hydrogels are intimately related. The fabrication technique usually dictates the polymerisation conditions. For example, IPN preparation requires the presence of the substrate during polymerisation. The porosity of hydrogel systems depends on synthesis conditions and affects their mechanical and physical properties.

Table 2.4 gives a brief list of some of the biomedical applications of synthetic hydrogel. This table lists three categories of hydrogels: coatings, "homogeneous" materials, and devices. The wide range of biomedical applications of hydrogels can be attributed to both their satisfactory performance upon *in vivo* implantation in either blood-contacting or tissue-contacting situations and their ability to be fabricated into variety of morphologies.

Table 2.4 : A brief list of the biomedical applications of synthetic hydrogels [13].

Coatings	"Homogeneous" Materials	Devices
Sutures	Electrophoresis gels	Enzyme therapeutic
Catheters	Contact lenses	systems
IUDs	Artificial corneas	Artificial organs
Blood detoxicants	Vitreous humor replacements	Drug delivery systems
Sensors (electrodes)	Estrous - inducers	
Vascular grafts	Breast or other soft tissue	
Electrophoresis cells	substitutes	
Cell culture substrates	Burn dressings	
	Bone ingrowth sponges	
	Dentures	
	Ear drum plugs	
	Synthetic cartilages	
	Hemodialysis membranes	
	Particulate carriers of	
	tumor antibodies	

2.7 Perceived Advantages of Hydrogels as Biomaterials [18]

Interest in hydrogels as biomaterials stems from a number of real and hypothesized advantages for these polymers:

(a) The expanded nature of the hydrogel structure allows extraneous, low molecular weight materials incorporated during preparation to be thoroughly washed out, leaving only the pure, insoluble gel network.

(b) The soft, rubbery nature of hydrogels minimizes mechanical and frictional irritation to surrounding tissue.

(c) These polymers may have low or zero interfacial tension with surrounding biological fluids and tissue, thereby minimizing the driving force for protein adsorption and cell adhesion.

(d) hydrogels allow the permeation and diffusion of low molecular weight metabolites, waste products and salts , as does living tissue.

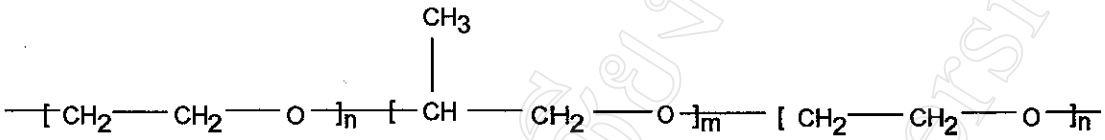
The importance of most of these factors for biocompatibility has never been clearly demonstrated. However, it is well known that the leaching of toxic materials from implanted biomaterials can cause inflammatory reaction (see item (a) above) and that the matching of the mechanical modulus of a polymer to that of the surrounding tissue may be important for biocompatibility (see item (b) above).

2.8 Application of Synthetic Hydrogels as Wound Dressings [28,29]

The development of synthetic occlusive wound dressings used for the treatment of burns, granulation tissue, dermatitis, ulcerations, blisters, fissures, herpes, and several other skin conditions is currently a subject of great commercial interest. Work on wound coverings has been in progress since the last century. It is appropriate to be reminded of the properties that a successful wound dressing material should possess. The material should be flexible, non-antigenic, strong, and permeable to water vapour and metabolites, whilst securely covering the wound to prevent bacterial infection. A wound dressing known as **Op-site** based upon P(HEMA) and an elastomeric polyurethane was found to reduce pain and speed healing. However, fluid accumulation underneath the dressing, probably related to the low permeability of the material, was found to be a problem.

An alternative approach was provided by **Pluronic F-127**, a block copolymer of polyoxypropylene glycol and ethylene oxide, with the water-soluble oxyethylene chains (70%) at the ends and insoluble oxypropylene chains (30%) in the center (see structure below). A 20% aqueous solution of Pluronic is clear, non-toxic and liquid at low temperatures. This solution can be poured easily onto the burn site and has been used successfully as a burn dressing on rats [30]. However, at body temperature, it forms a clear gel which fills the crevicies in the wound and isolates the area from bacterial infection. The gel reverts to a liquid at low temperatures because of increased solubility due to hydrogen bond formation; therefore, the dressing can easily be removed by washing it with cold water. The Pluronic gel can also be used as a base for anti-bacterial agents (e.g., silver nitrate or silver lactate), the normal loading being 0.5% nitrate or lactate suspended in Pluronic [31]. Further work with rats has shown that the use of a Pluronic gel containing an anti-bacterial agent is effective in

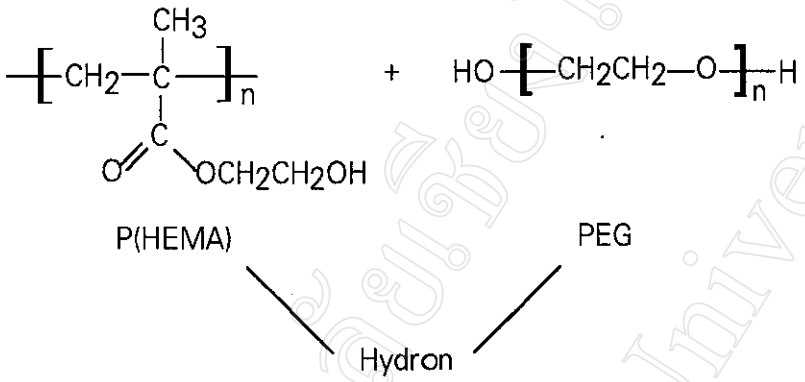
reducing the mortality rate by 75% for rats with an infected 20% full thickness burn. Recent work with burns on porcine skin (which is similar to human skin) suggested that Pluronic F-127 may stimulate the production of epithelial growth factor. Additionally, the rate of healing of the Pluronic treated burns after 30 days was significantly increased.



Pluronic F-127

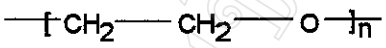
One of the most widely studied synthetic hydrogel-based wound dressings is the **Hydron** Burn Bandage. The dressing is formed directly on the burn wound from a two-component system, solid P(HEMA) with liquid polyethylene glycol (PEG) as the solvent. Alternate layers of PEG and P(HEMA) are applied to the wound, either by spraying the components from a compressor or by direct application of PEG and powdered P(HEMA), until three or four layers have been built up. The PEG dissolves the P(HEMA) forming a saturated solution which forms a solid film after 30 mins. The disadvantages of Hydron are that it is difficult to apply, does not adhere well to the wound, especially if it is moist, and that cracking of the film is a problem in a significant number of cases. Additionally, as the dressing is translucent, it is not possible to visually monitor the wound healing and the dressing must be cut away to check the wound for infection. However, several other clinical studies have reported promising results using Hydron [32]. It has been described as a "valuable asset" in the treatment of burns which is easy and painless to apply and reduces the pain for the patient after application. Hydron is also fairly flexible and, although its tensile

strength is relatively low, the translucent dressing can remain in place for up to a week between changes. In addition, the permeability of Hydron enables the problem of infection in the wound to be overcome by loading the dressing with an antibacterial agent.



A primary wound dressing based on a poly(ethylene oxide) hydrogel, **Vigilon**, has also had extensive clinical trials. Vigilon is a colloidal suspension of radiation crosslinked polyethylene oxide and water with an equilibrium water content of 96%, sandwiched between two polyethylene films. It is permeable to oxygen, will absorb exudate from the wound, is non-adhesive to tissue, impermeable to bacteria, and virtually transparent [33]. To apply the dressing, the polyethylene film from the side of the dressing placed on the wound is removed, leaving the film on the other side intact. In studies with pigs, it was found that the healing time of wounds dressed with Vigilon was shorter than the air exposed controls; the Vigilon dressed wounds having a 44% increase in re-epithelization compared to the controls. In clinical trials, treatment with Vigilon has led to increased periods between dressing changes with decreased patient discomfort. It has proved very useful in the treatment of scalds on

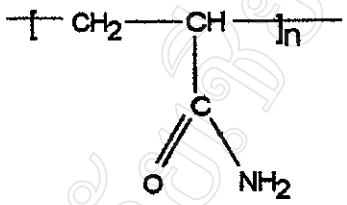
children and partial thickness burns where it appears to improve wound healing [33]. Vigilon was used in the treatment of various wounds including dermabrasions, sutured surgical incisions and hair transplants. The study concluded that treatment with Vigilon increased the healing rate and all wounds treated with Vigilon were also found to be free of infection. If Vigilon is impregnated with povidone-iodine, it enhances the advantages of occlusive wound dressings, while protecting the wound from bacterial infection.



poly(ethylene oxide)

A novel hydrogel dressing, **Geliperm** was developed by the Max Planck Institute for Immunobiology and Dermatology. Geliperm is synthesised from acrylamide and agar, the acrylamide being crosslinked in a solution of agar using N' N'- methylene-bis-acrylamide as a crosslinking agent to produce an interpenetrating polymer network [34]. The gel has as equilibrium water content of 96% but is extremely elastic with a high tensile strength of 247 N/cm^2. Geliperm is permeable to oxygen, water vapour, and proteins, with a molecular weight of up to 1,000,000 but is impermeable to bacteria and cells. It is available in smooth, transparent (hydrated or dehydrated) sheets, is non-immunogenic, non-toxic and will absorb any exudate from the wound. A more detailed examination of the properties and uses of Geliperm was given by Myers [35]. Geliperm is also available in granular form which is useful in the treatment of deep fissured wounds. The granular form has a much larger surface area than Geliperm film and, therefore, is able to absorb large amounts of exudate. Granular Geliperm also has the ability to absorb bacteria between the granules making

it an ideal method of removing bacteria from contaminated wounds. Clinical trials with Geliperm show that it improves the rate of wound healing and is easy to apply and remove without causing pain to the patient. The dressing can be changed without damaging the new skin being formed beneath it.



polyacrylamide

Finally, a composite hydrogel wound dressing, **Omiderm**, has been synthesised by grafting acrylamide onto a polyurethane film to give a transparent, flexible gel with an equilibrium water content of approximately 50% [36]. The hydrated gel has a low modulus of elasticity, which improves the adherence of the gel to the wound, and high water permeability. Omiderm was found to have a higher permeability to antimicrobial agents than other occlusive dressings and its effectiveness as a base for antimicrobial agents was confirmed *in vivo*. Clinical trials on burns, ulcers, and graft donor sites confirmed the potential of Omiderm as a wound dressing [37] although, in some burn wounds, fluid was found under the dressing.