CHAPTER 2

BIOMEDICAL APPLICATIONS OF HYDROGELS

2.1 Introduction [5]

The earliest uses of hydrogels in medicine involved natural tissue which, for all practical purposes, can be categorized as a hydrogel. Cellulose (sausage casing) behaves as a hydrogel and has also had a long history of use in medicine, particularly in hemodialysis applications. However, the conceptualization and initial development of synthetic, polymeric hydrogels designed specifically for biomedical applications has generally been attributed to Wichterle and Lim [6]. In their article published in 1960 [6], 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 an extensive review on hydrogels published in 1976 [7], a number of questions and problems concerning hydrogel systems were raised. The following section provides a brief description of the chemistry, physical properties, and applications of hydrogel materials.

2.1.1 Definitions [8,9]

The simplest definition of a hydrogel is "**a network which swells in water**". According to another definition, a hydrogel can be defined as a polymer material possessing ability to swell in water and retain a significant fraction of water within its structure, but which will not dissolve in water. The definition offered by Silberger [8] is still more detailed, taking into account the potential instability of the system formed by the swollen network and its surroundings where the temperature, pressure or chemical composition of the surroundings is changed. Hence, hydrogels are

characterized by a pronounced affinity of their chemical structure towards water in which they do not dissolve, but merely swell. This is due to the existence of crosslinks which, at least in water, bind macromolecules or their segments either by permanent bonds (definite chemical links) or through more extensively organized regions (effective crosslinks). The latter are formed by bonds of sufficiently long life that changes in structure do not occur, or only occur very slowly under stress. In water, they swell to an equilibrium volume, but preserve their shape. The polymer's hydrophilicity is due to the presence of water-solubilizing groups in its chemical structure, such as :

$-OH$

$-COOH$

$-CONH_2$

$-CONH-$

$-SO_3H$

Alternatively [5], hydrogels have been defined as materials which have the following properties in common:

(a) they are comprised of polymeric chains

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

(c) they will swell to an equilibrium value of (typically) 10 to 98% H_2O at physiologic temperature, pH and ionic strength

The ***water content*** (% H_2O) of the polymer is defined as:

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

2.1.2 Factors Affecting the Swelling of Hydrogels [5]

The factors which influence the swelling of hydrogels can be divided into two groups: those which are favourable to the entrance of water into the polymer structure and those which resist or inhibit the water influx. Some of these factors are summarized below :

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

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. Strong positive interactions between chemical structures in the polymer and the water (e.g., hydrogen bonding) will further increase the driving force for swelling. As water enters the polymer, the polymer chains which are (in most cases) in an equilibrium configuration, are extended. This is illustrated schematically in Fig. 2.1. Fig. 2.1 (a) represents the most entropically favourable configuration given the mechanical constraints of the polymer chain. The entrance of water into the system will necessitate its expansion and consequent ordering of the polymer chain as shown in Fig. 2.1 (b). Since the chains will be elongated into less entropically desirable configurations, they exert a resistive force. When the osmotic force driving water into the system is balanced by the force exerted by the polymer chains in resisting expansion, at that point, the ***equilibrium degree of swelling*** will have been achieved.*

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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.

Increased crosslink density (a shorter distance between crosslink points) will have the effect of increasing the resistive force to chain elongation. Consequently, more highly crosslinked systems demonstrate lower degrees of equilibrium swelling [10]. 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 sufficiently low, bulk water may be unable to penetrate into the polymer matrix to initiate the swelling process.

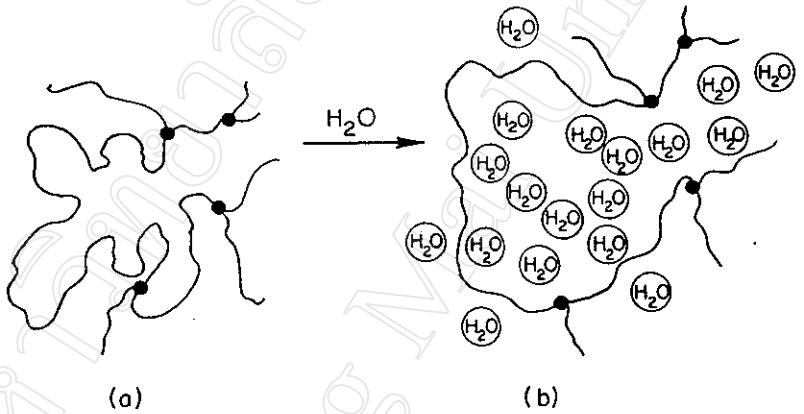


Fig. 2.1 : Water entrance into a single, idealized hydrogel chain segment.

A quantitative description of swelling in crosslinked polymers formed in the swollen state has been developed [11] and applied to hydrogel systems. An equation to express this swelling, derived from a statistical description of polymer equilibrium configuration and incorporating a factor to account for the extent of chemical interaction between polymer and solvent, can be written in the form :

$$-\ln(1-v_2) - v_2 - \chi v_2^2 = \nu V_1 (\langle \alpha_o \rangle^2 v_2^{1/3} - \frac{v_2}{2}) \quad (2)$$

where v_2 = volume fraction of polymer in the swollen network
V_1 = molar volume of the swelling liquid
χ = Flory–Huggins interaction parameter between polymer and solvent (interaction energy per solvent molecule divided by kT)
ν = network (crosslink) density
$\langle \alpha_o \rangle$ = dilation factor in the absence of solvent

Although the practical application of this equation (2) is outside the scope of this project and will not be discussed further, it is shown here in order to illustrate the fact that the swelling of a polymer by a solvent is a true thermodynamic process for which a sound underlying theory has been developed. This theory has contributed much to our current understanding of polymer–solvent interactions in crosslinked systems.

2.2 Synthetic Hydrogels and Their Fabrication

Many different chemical structures can be classified as hydrogels. A number of such polymeric compounds are illustrated in Table 2.1 [5,12]. When fabricated into hydrogels, they will not dissolve in aqueous media because the polymer chains are interconnected (crosslinked), either by covalent bonds or noncovalent interactive forces.

Hydrogels are fabricated into useful forms using a variety of techniques. The specific technique used is primarily dependent upon the nature of the polymer. However, the objectives in all cases are the same: to prepare a hydrophilic polymer which maintains its integrity in water, which is in precise geometric configuration for the required application and which has sufficient mechanical strength and appropriate compliance to make it useful for that application. Hydrogel systems prepared by various methods are illustrated schematically in Fig. 2.2. Cast films (Fig. 2.2A), frequently used as coatings for other materials, usually require noncovalent forces (e.g., hydrophobic bonding) to prevent dissolution of the polymer in aqueous media. However, in many cases, films can be covalently crosslinked

after casting. Crosslinked hydrogel networks (Fig. 2.2B) are generally formed by injecting into a mould a mixture of monomer, crosslinking agent and initiator. A solvent is also added to this mixture in some instances. The surface grafting of hydrogels to another polymer (Fig. 2.2C) is attractive as a fabrication technique for a number of reasons : the hydrophilic polymer is made insoluble by bonding to an insoluble substrate, the generally low mechanical strength of hydrogels is improved by bonding to a mechanically strong polymer, and fabrication is simplified since only the substrate need be formed into a specific shape. The graft then follows the contours of the substrate polymer. Crosslinked hydrogel networks can also be formed within other polymer networks (Fig. 2.2D). Both networks are topologically independent and inseparable. This interpenetrating polymer network (IPN) approach represents another technique for mechanically strengthening hydrogel systems [13,14]. Finally, hydrogels can be formed as uniform microspheres in sizes ranging from 0.3 μm to 3.4 μm [15].

Table 2.1 : Chemical structures of some polymers used in synthetic hydrogels [5, 12].

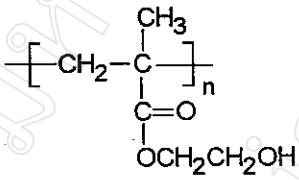
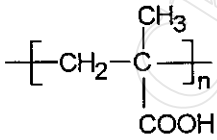
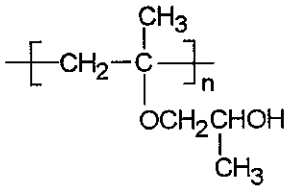
Chemical Structure	Polymer Name
	poly(2–hydroxyethyl methacrylate)
	poly(methacrylic acid)
	poly(2–hydroxypropyl methacrylate)

Table 2.1 : (continued)

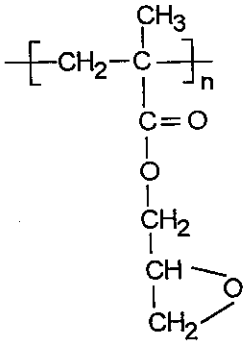
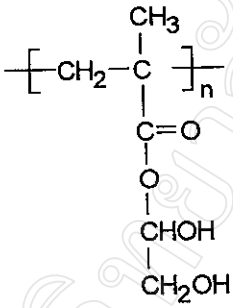
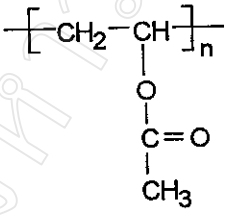
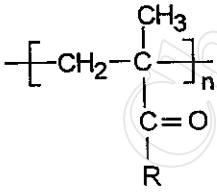
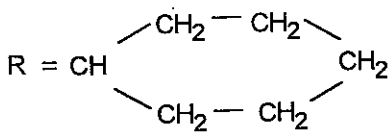
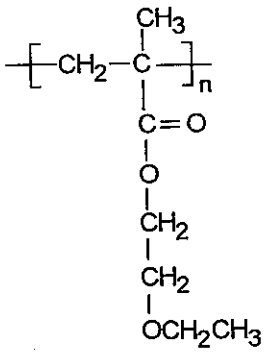
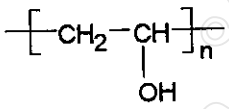
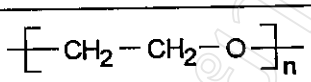
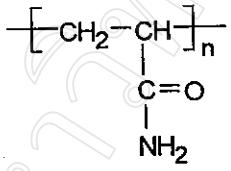
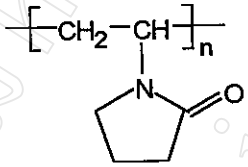
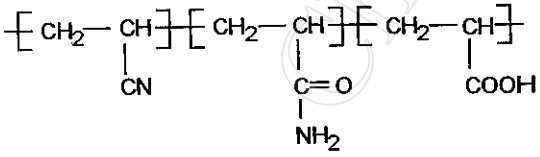
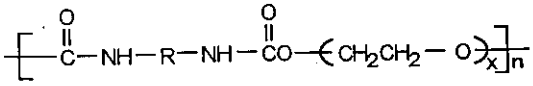
Chemical Structure	Polymer Name
	poly(glycidyl methacrylate)
	poly(glyceryl methacrylate)
	poly(vinyl acetate)
	poly(alkyl methacrylate)
R = CH_3	poly(methyl methacrylate)
R = $CH_2CH_2CH_2CH_3$	poly(butyl methacrylate)
R = 	poly(cyclohexyl methacrylate)

Table 2.1 : (continued)

Chemical Structure	Polymer Name
	poly(2–ethoxyethyl methacrylate)
	poly(vinyl alcohol)
	poly(ethylene oxide)
	poly(acrylamide)
	poly(N–vinyl pyrrolidone)
	hydrolyzed poly(acrylonitrile)
	polyurethane based on poly(ethylene oxide)

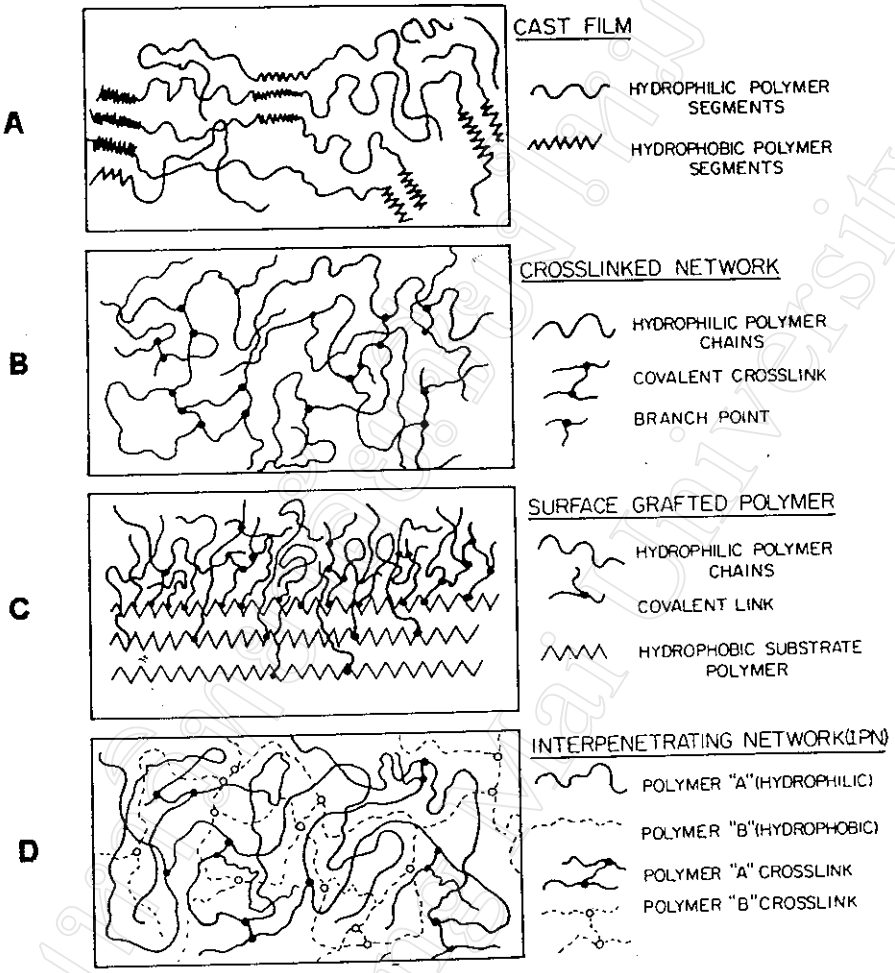


Fig. 2.2 : Methods of fabrication of hydrogels [9].

2.3 The Hydrogel – Water Interface [9]

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 finally to bulk water, as shown in Fig. 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 proportion 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 which have been used to study the hydrogel–water interface include ESCA [16], contact angle measurements [17,18], and hydrodynamic flow studies [19]. 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 [17], and that the surface is microscopically deformable under flow. Still, a true molecular picture of this interface has yet to be developed. Its significance for biological interaction remains to be elucidated.

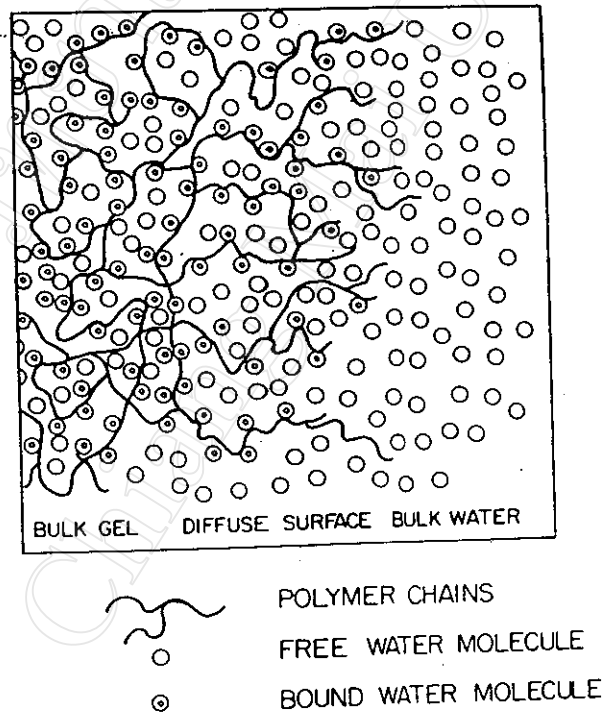


Fig. 2.3 : Schematic representation of the hydrogel–water interface.
(Structured water is not shown in this diagram. Regions of structured water might be expected in the vicinity of the bound water molecules due to their strong, fixed dipoles.)

2.4 The Advantages of Hydrogels as Biomaterials

The 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 fluid 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 and that the matching of the surrounding tissue may be important for biocompatibility.

2.5 The Viscoelastic Behaviour of Hydrogels [8]

Assuming that part of the water in the hydrogel is highly structured, it is possible to describe the osmotic, swelling, and viscoelastic behaviour of gel networks in terms of a solubility theory modification to the classical Flory theory. In describing the viscoelastic behaviour of hydrogels, three functions, governed by the three types of water, are used to explain the stress–strain relations in the rubbery region :

2.5.1 Effect of Pressure

The elastic contractability creates a force counteracting the penetration of the water into the hydrogel. It is understandable, therefore, that the equilibrium degree

of swelling depends on the degree of compression of the gel under a mechanical pressure. Under certain circumstances, water exudes from the swollen hydrogel until equilibrium is reached. Highly hydrated hydrogels (jellies, over 90% water) lose much water with comparatively low compression, sometimes with only the pressure of their own weight. This occurs with some hydrogels of poly(2,3–dihydroxypropyl methacrylate). Hydrogels of poly(2–hydroxyethyl methacrylate), which, in the equilibrium swelling condition contain about 40% water, may also lose water due to long–term compression, but the pressures required are much higher.

2.5.2 Effect of Ionizable Groups

Polymer networks which behave as hydrogels but contain ionizable groups behave in a more complex way. Swelling of such hydrogels depends on the degree of ionization of the groups. This is known especially for carboxylic groups, notably in copolymers of acrylic or methacrylic acid. Basic groups also affect the degree of swelling but to a lesser extent.

2.5.3 Permeability

The permeability of poly(2–hydroxyethyl methacrylate) membranes has been studied by several authors [20–22]. It is generally accepted that the structure of membrane–forming gels depends on the amount of the crosslinking agent used. "Voids" (minute pores) are present, making possible the transport of water and solutes. The membrane then acts as a sort of network. At high concentrations of crosslinks, the minute pores are not formed, or they are already too small. The transport of water and of relatively small molecules is, however, still possible by employing the partition of dissolution mechanism. Under certain circumstances, both mechanisms can operate. The presence of "voids" of free volume also explains why, at the beginning of swelling of dry hydrogels, a much greater initial amount of water is taken into the gel than would be anticipated from the linear swelling measurement alone. It appears that the pores are quickly filled with water before the gel is able to produce any linear expansion. This view has also been adopted for some biopolymers [23].

2.6 Application of Hydrogels as Burn Dressings [24 – 26]

With over 2 million burn injuries occurring each year in the U.S. alone, the development of improved burn dressings represents an important and commercially viable area for investigation. Among the most successful dressings for treating severe burns in their early stages of healing are human or porcine skin [2]. However, synthetic materials exhibiting simplified preparation prior to application, improved ease of application, greater uniformity, and superior performance would be desirable. Some of the synthetic hydrogel materials which have been developed for this purpose are now described.

It has been appreciated for some time that synthetic hydrogels, such as ***poly(2–hydroxyethyl methacrylate)***, P(HEMA), may be suitable for general prosthesis applications. Hydrogels are employed as prostheses in a number of forms ranging from homogeneous, optically transparent films to composite structures such as non–porous gels, porous sponges and thromboresistant coatings bound to a less biotolerant polymer substrate. One of the earliest examples of such forms involves P(HEMA) in the form of a spongy gel used in breast augmentation. The consistency of such gels can be tailored to give an elasticity that is comparable with that of the original tissue. In addition, P(HEMA) has the potential advantage over alternative materials that have been used, such as poly(methyl methacrylate), polyethylene and silicones, in that it does not provide a barrier to the transfer of body fluids from the surrounding tissue. This permeability to low–molecular weight metabolites and ions may be advantageous to performance *in vivo*. A follow–up of the patients that received the hydrogel implants showed no change in either the implants or the surrounding tissues. Against this evidence, however, must be set the results of long–term studies with P(HEMA) implanted subcutaneously in rats, hamsters and guinea–pigs, which appeared to show the material to be tumorigenic and susceptible to calcification. This work suggests that P(HEMA) is more suited to short–term applications such as a temporary skin substitute rather than as a long–term implant material.

Hydrogel materials have been considered in a number of instances for burn dressings. ***Poly(vinyl alcohol) synthetic sponge*** was utilized for this purpose almost 20 years ago [27]. Despite initially encouraging reports with this material,

results were, in general, poor due to bacterial invasion, late stiffening of the film, and adhesion of fragments of the sponge in the wound bed. A wound dressing known as ***Op-site*** based upon P(HEMA) and an elastomeric polyurethane was found to reduce pain and accelerate healing [28]. However, fluid accumulation underneath the dressing, probably related to the low permeability of the material, was found to be a problem. An ingenious hydrogel burn dressing based upon a block copolymer of poly(propylene oxide) and poly(ethylene oxide), ***Pluronic F 127***, was applied as a water solution which subsequently gelled due to reduced solubility of the polymer at body temperature [29]. The material was found to be easy to apply and electrolyte imbalance, heat loss, and bacterial invasion were minimized. Despite this, further investigation of this material for burn dressing applications has not been reported and ***Pluronic F 127*** is apparently no longer being manufactured.

There have been at least two attempts to develop burn dressing materials based upon ***P(HEMA) radiation–grafted to silicone rubber sheeting*** [30,31]. Silicone rubber has a number of desirable qualities for burn dressings including strength, low biological reactivity, and excellent gas permeability. However, its poor adhesion to regenerating granulation tissue has prevented its use as a burn dressing. By modifying the surface properties of the silicone rubber, improvements in wound adhesion were expected. Many of the parameters involved in producing radiation–grafted materials for wound covering applications including radiation dose, crosslinking agent concentration, and substrate (***Silastic***) thickness were explored [31]. The radiation–grafted P(HEMA) was found to have little effect on the water vapour permeability of the ***Silastic*** substrate. The water vapour permeability of the graft rubber was similar to that of remoistened freeze–dried skin. The hydrophobic ***Silastic*** surface was converted by this treatment from nonwettable to wettable, presumably a desirable transformation for wound adhesion. In an evaluation of the performance of a variety of synthetic wound dressing materials, radiation–grafted ***P(HEMA)/Silastic*** dressings were found to have the lowest overall composite score reflecting their low wound adhesion, relatively low water vapour transmission, and smooth surface texture [32].

A new burn and wound dressing based upon P(HEMA) and poly(ethylene glycol) has recently been developed [32] under the trade name ***Hydron***. The manner of application of this dressing is quite unique. Liquid poly(ethylene glycol)

(M.W. = 400) is first delivered to the wound surface with a syringe and evenly dispersed with a swab. Powdered uncrosslinked P(HEMA) is then dusted over the wound surface. The P(HEMA) dissolves in the poly(ethylene glycol). In about 30 minutes, the mixture forms a solid film. The advantages of this dressing are excellent adhesion to the wound surface, moderate flexibility and strength, and transparency enabling the wound surface can be examined. Also, topical antibiotics can be applied directly through the ***Hydron*** dressing. The dressing can be applied prior to the sloughing or removal of the burn wound eschar, a period during the burn therapy for which alternative dressings are not readily available. Decreased frequency of dressing changes with ***Hydron*** results in reduced patient discomfort. Healing under the dressing proceeds similarly to that seen for conventional dressings with no evidence of fluid accumulation or maceration or desiccation of the eschar.

A wound dressing based on a poly(ethylene oxide) hydrogel, ***Vigilon***, has also had extensive clinical trials [26]. ***Vigilon*** is a colloidal suspension of radiation–crosslinked poly(ethylene 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, impermeable to bacteria, non–adhesive to tissue, and virtually transparent. 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 a wound dressed with ***Vigilon*** was shorter than the air–exposed control, the ***Vigilon*** dressed wounds showing a 44% increase in re–epithelization compared to the control. 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.

Another novel hydrogel dressing, ***Geliperm***, has been developed by the Max Planck Institute for Immunobiology and Dermatology. ***Geliperm*** is synthesized 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. ***Geliperm*** has many properties which make it an almost ideal wound dressing material. The gel has an 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 impermeable to bacteria and cells. It is available in smooth, transparent sheets, is non–toxic, non–immunogenic and will absorb any exudate from the wound. ***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 is therefore 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. ***Geliperm*** is easy to apply and remove without damaging the new skin being formed beneath it and, for this reason, ***Geliperm*** has proved useful in skin grafting, increasing the chance of the graft healing.

A composite hydrogel wound dressing, ***Omiderm***, has been synthesized by grafting acrylamide onto a polyurethane film to give a transparent, flexible gel with an equilibrium water content of approximately 50%. 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 (ex. ***Op–Site***) and its effectiveness as a base for antimicrobial agents was confirmed *in vivo*. However, in some burn wounds, fluid was found under the dressing. One explanation for this was that the pores in ***Omiderm*** were blocked by particles from the wound.