CHAPTER II

BACKGROUND AND LITERATURE REVIEWS

2.1 Hydrogels

Hydrogels are water-swollen, crosslinked polymeric structures containing either (i) covalent bonds produced by the simple reaction of one or more co-monomers, (ii) physical cross-links from entanglements, or (iii) association bonds such as hydrogen bonds or strong van der Waals interactions between chains or crystallites bringing together two or more macromolecular chains. Hydrogel can swell up to thousands of times of their dry weight, but do not dissolve when brought into contact with water or aqueous solution. In the swollen state they are soft and rubbery. Hydrogels have received significant attention because their distinctive material structures make them suitable for a wide range of applications in modern robotic systems, tissue engineering, and therapeutic delivery[16] (Figure 2.1). More recently, polymer hydrogel composites have been synthesized and characterized for electro-chemically controlled drug release devices.[17]

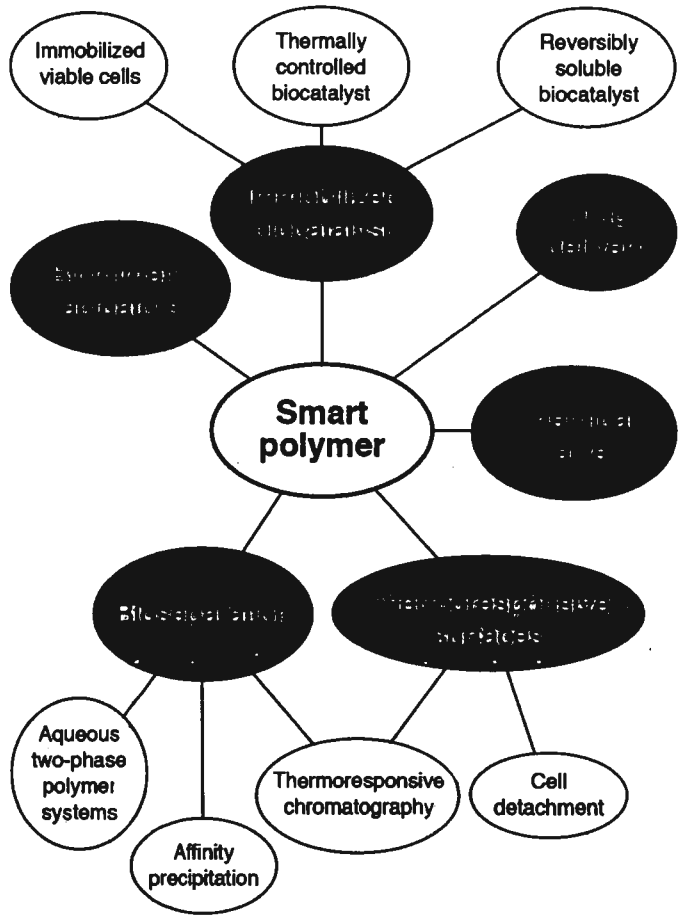


Figure 2.1 Uses of smart polymers in biotechnology and medicine[18]

2.1.1 Classification and Basic Structure

Depending on method of preparation, ionic charge, or physical structure features, hydrogels may be classified in several categories. Based on the method of preparation, they may be (i) homopolymer hydrogels, (ii) copolymer hydrogels, (iii) multipolymer hydrogels, or (iv) interpenetrating polymeric hydrogels.[19]

Homopolymer hydrogels are cross-linked networks of one type of hydrophilic monomer unit, whereas copolymer hydrogels are produced by cross-linking of two co-monomer units. At least one of them must be hydrophilic to render them swellable. Multipolymer hydrogels are produced from three or more co-monomers reacting together. Finally, interpenetrating polymeric hydrogels are

produced by preparing the first network that is then swollen in a monomer. The latter reacts to form the second intermeshing network structure.

Based on their ionic charges, hydrogels may be classified as (i) neutral hydrogels, (ii) anionic hydrogels, (iii) cationic hydrogels, or (iv) ampholytic hydrogels.

Based on physical structural features of the system, they can be classified as (i) amorphous hydrogels, (ii) semicrystalline hydrogels, or (iii) hydrogen-bonded or complexation structures. In amorphous hydrogels, the macromolecular chains are arranged randomly. Semicrystalline hydrogels are characterized by dense regions of ordered macromolecular chains (crystallites). Finally, hydrogen bonds and complexation structure may be responsible for the three-dimensional structure formed.

Structural evaluation of hydrogels reveals that ideal networks are rarely observed. Figure 2.2A shows an ideal macromolecular network (hydrogel) indicating tetrafunctional cross-links (junctions) produced by covalent bonds. However, in real networks it is possible to encounter multifunctional junctions (Figure. 2.2B) or physical molecular entanglements (Figure. 2.2C) playing the role of semipermanent junctions. Figure 2.2D and 2.2E indicate two such effects: unreacted functionalities with partial entanglements (Figure. 2.2D) and chain loop (Figure. 2.2E). Neither of these effects contributes to the mechanical or physical properties of a polymer network.

The term "cross-link," "junction," or "tie-point" (an open circle symbol in Figure. 2.2D) indicate the connection points of several chains. These junctions may be carbon atoms, but they are usually small chemical bridges (e.g., an acetal bridge in the case of cross-linked poly(vinyl alcohol)) with molecular weights much smaller than those of the cross-linked polymer chains. In other situations, a junction may be an association of macromolecular chains caused by van der Waals forces, as in the case of the glycoproteinic network structure of natural mucus, or an aggregate

formed by hydrogen bonds, as in the case of aged microgels formed in polymer solutions.

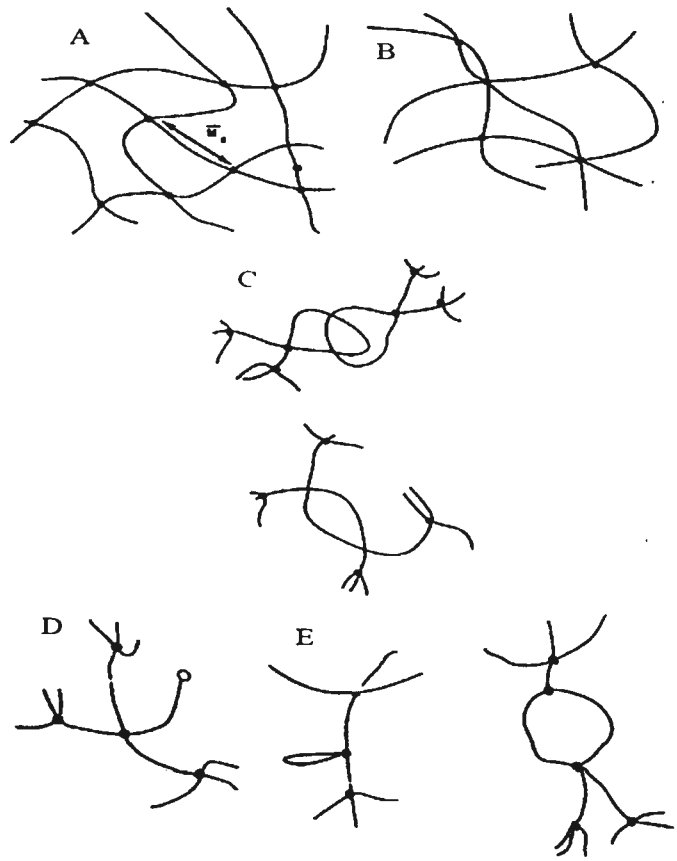


Figure 2.2 (A) Ideal macromolecular network of a hydrogel. (B) Network with multifunctional junctions. (C) Physical entanglements in a hydrogel. (D) Unreacted functionality in a hydrogel. (E) Chain loops in a hydrogel[19]

Finally, the network structure may include effective junctions that can be either simple physical entanglements of permanent or semipermanent nature, or ordered chains forming crystallites. Thus, the junctions should never be considered as points without volume, which is the usual assumption made when developing structural models for analysis of the cross-linked structure of hydrogels. Instead, they have a finite size and contribute to the deformational distribution during biomedical application. Ongoing investigations on hydrogels have established their potential for use in several fields, such as chemical engineering, foodstuffs, agriculture, medicine and pharmaceuticals (e.g. controlled drug delivery systems).

Also, they may have applications as muscle-like soft linear actuators, robotics, sensors, biomimetic energy transducing devices and separation techniques.[20]

The major disadvantage of hydrogels, low mechanical strength, can be overcome either by crosslinking in formation of interpenetrating polymer networks (IPNs), or by crystallization that induces crystallite formation and drastic reinforcement of their structure.

2.1.2 Intelligent or Smart Material

Hydrogels have attracted attention as "intelligent material" or "smart material" because of their peculiar material forms. They consist of an elastic crosslinked network and a fluid filling the interstitial spaces of the network.[21]

Many smart materials are made of polyelectrolytes, they can change their shape and volume reversibly dependent on several environmental stimuli. Over the past 30 years there has been a significant interest in the development and analysis of environmentally or physiologically responsive hydrogels. Environmentally responsive materials show drastic changes in their swelling ratio due to changes in their external ionic strength, temperature, pH, nature and composition of the swelling agent, light (ultraviolet or visible), enzymatic or chemical reaction, and magnetic or electrical stimuli. These phenomena can directly transform chemical free energy into mechanical energy in response to environmental stimuli that referred to as a "chemomechanical system". The magnitude of the deformation and the response time of these hydrogel networks are affected by various parameters, including the molecular weight and the conformation of the polymer chains composing the network, the hydrophilicity of the polymer network, the size and the functionalities of the monomers employed, as well as the charge density of the polymer chains forming the polymeric network. Therefore, hydrogels offer the possibility of various advanced functional polymers. The stimuli-responsive hydrogels, actuated by an electric field,

seem to be particularly interesting because they may be incorporated with a modern robotic control system.

2.1.3 Electro-sensitive hydrogels

Electro-sensitive hydrogels are normally made of polyelectrolytes and an insoluble, swellable, polymer network containing ionic groups. The response of electro-sensitive hydrogels generally exhibits in the form of either swelling/shrinking or bending behaviors. Several research groups have extensively studied the mechanism of such behaviors in the last two decades. Tanaka and his coworkers reported that a rod-like specimen of a copolymer of an acryl acid–acrylamide gel contracted at its anode side when it was placed between electrical electrodes[22]. They interpreted such an effect as an electric field pushed a negatively charged gel toward an anode and squeezed the anode side of the hydrogel. However, such interpretation was questioned when Shiga and Kurauchi proposed that this effect may be induced by the change in the ionic distribution under an electric field[23]. Later in 1992, Doi et al. proposed a semi-quantitative theory to explain the swelling and shrinking behavior of a hydrogel under an electric field. They calculated the changes of ion concentration profile within the hydrogel[24]. Such a theory takes account of ion transports and electro-chemical reactions and combines the computational results with Flory's theory. Similar mechanisms were also proposed by several investigators.[25-27]

2.2 Chitosan

Chitosan, a transformed oligosaccharide, is obtained by deacetylation of chitin in a strong alkali solution, the latter being a bio-polymer obtained from invertebrate animals and lower plants. It is noticeably present in outer skeletons of arthropods in particular, for example, in the epidermis of crustaceans such as crabs and shrimp shells. In plants, chitin is present in hyphae or spores of molds. Chitin is a pure polymerized form of N-acetyl glucosamine. It has drawn more attention than other

bio-polymers because of its ability to form specific complexes with number of ions or dyes as well as specific complexes with organic molecules

2.2.1 Structure of Chitosan

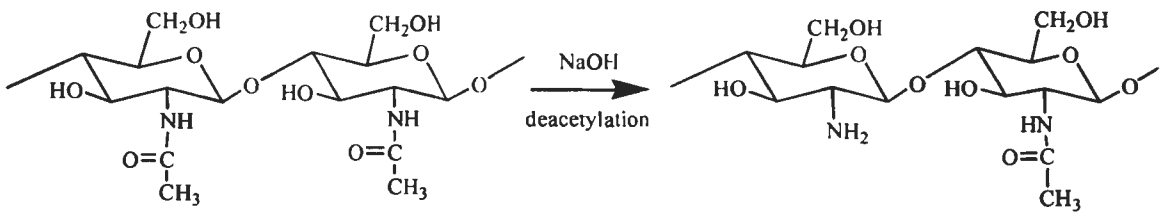


Figure 2.3 Chemical structure of chitosan

Chitosan $(C_6H_{11}O_4N)_n$, a natural linear biopolyaminosaccharide, is a copolymer of β-[1-4]-linked 2 –acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose[28] (Figure 2.3). A fraction of the repeating units in the chitosan backbone contains -NH_2 pendant groups while the rest contains acetamide group (-NHCO-) in its place. The degree of deacetylation can be controlled by time, temperature and concentration of alkaline treatment of chitin.[29] Chitosan has both reactive amino and hydroxyl group that can be used to chemically alter its properties under mild reaction conditions. The polymer differs from chitin in that a majority of the N-acetyl groups in chitosan are hydrolyzed. The degree of hydrolysis (deacetylation) has a significant effect on the solubility and rheological properties of the polymer. Chitin and chitosan are practically insoluble in many of the organic or inorganic compounds, but soluble in salt organic mixtures of LiCl-NJ-DMAc[30], and dilute acids (water-acid mixtures) and gets precipitated in alkaline solution or polyanions. Thus, there have been many interesting chitosan derivatives, especially for biomedical applications. For these uses, the key properties of chitosan are its biocompatibility, bioactivity, nonantigenicity, nontoxicity (its degradation products are known natural metabolites), the ablility to improve wound healing and/or blood cloating, the ability to absorb liquids and form protective films and coatings and its selective binding of liquids, which has been used to lower serum cholesterol levels.

2.3 Poly(acrylic acid)

Acrylic acid has served, for more than 30 years, as an essential building block in the production of some of our most commonly used industrial and consumer products. Acrylic monomers are highly reactive chemicals and, therefore, are useful, nearly exclusively as intermediates in the production of other materials. Acrylic acid is used to produce polyacrylic acid, or crosslinked polyacrylic acid compounds, which have been successfully used in the manufacture of hygienic products, detergents, and waste water treatment chemicals.

2.3.1 Structure of Poly(acrylic acid)

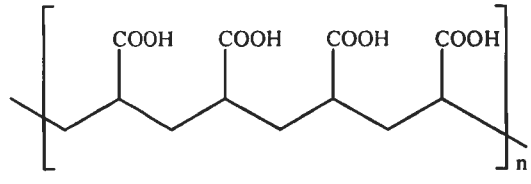


Figure 2.4 Chemical structure of poly(acrylic acid)

Poly(acrylic acid) (PAA) (Figure 2.4), a typical polyelectrolyte, is particularly useful for sensing and modulating external chemical signals, because its chain conformation is sensitive to pH, ionic strength of the aqueous media and electrical sensitive materials due to ionic repulsion between anionic charged groups, and thus forms polymer complexes with polybases such as poly(ethylene oxide), polyvinylpyrrolidone, polyacrylamide, or chitosan. PAA has been used as additive in biomimetic or sol-gel preparations for several purposes: in some cases, it is used as nucleating calcium-binding sites through its carboxy groups. In other cases, PAA is used as calcification inhibitors as it can bind to growing crystal faces avoiding their growth.[31]

2.3.2 Deformation of poly(acrylic acid) in electric fields

PAA was the first polyelectrolyte as an electroactive polymer gel.[32] Figure 2.5 shows the observed deformation of a poly(sodium acrylate) gel, (PAA) gel, with a negatively charged network in aqueous solution under the influence of a direct-current (DC) electric field. The type of deformation induced by a DC electric field depends on the pH of the surrounding solution, the salt concentration, the position of the gel relative to the electrodes, and the shape of the gel. The deformation of PAA gel, which is placed so as to touch the anode, involves only shrinking on the anode side in each solution.[33]

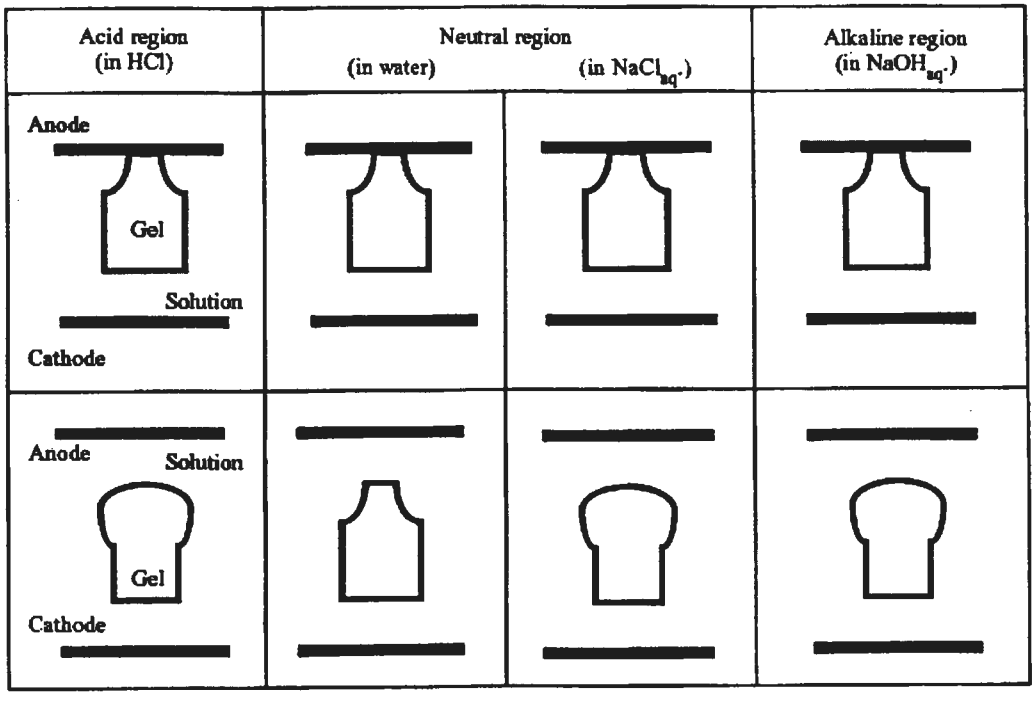


Figure 2.5 Deformation of poly(sodium acrylate) gel in DC electric fields[33]

When the gel is placed so as to be separated from the electrode, the pH of the solution affects the degree of deformation. In alkali and acid regions both gels swell on the anode side on application of a DC electric field. The deformation in neutral solutions is interesting. The ionic gel in water shrinks on the anode side, but swells and then shrinks in NaCl solution. The shape of gel also influences the deformation. When a rectangular gel is placed parallel to the electrodes, the electric field causes another type of deformation, bending.[34] This bending deformation may be due to the

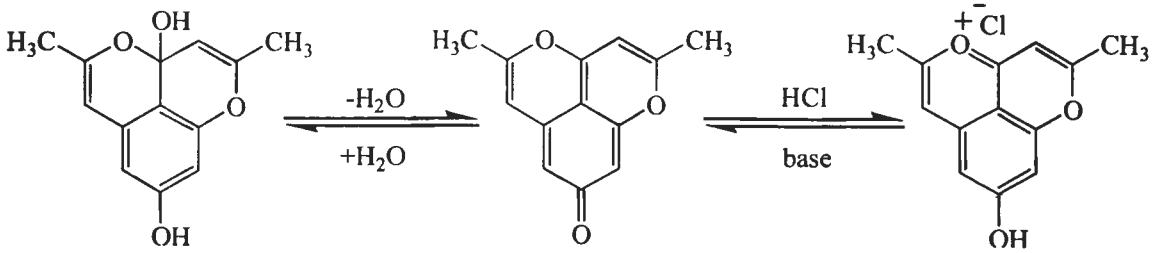
bimetallic principle of differential swelling or shrinking on the anode side. When a negative field is applied, the gel straightens at the same speed as the bending action. Because the deformation speed depends on the thickness, a thin gel will respond to AC electric fields of 0.5-2 Hz.

2.4 Barakol and its Chemical Nature

Cassia siamea is a plant widely cultivated in Southeast Asia (Figure 2.6). The different parts of the plant have been used as Thai traditional medicines[35-37], for example, for treatment of insomnia and various other medical conditions such as diabetes, hypertension, asthma, constipation and diuresis. *Cassia siamea* shows the physiological and pharmacological properties on the cardiovascular and central nervous systems.[38]

Figure 2.6 Features of Khilek tree *(Cassia siamea)*

Barakol (3a,4-dihydro-3a,8-dihydroxy-2,5-dimethyl-1,4-dioxaphenalene or 2,5-dimethyl-3 α H-pyrano[2,3,4-de]-1-benzopyran-3a,8-diol) (Figure 2.7), is a major active constituent extracted from the leaves and flowers of *Cassia siamea*. It was first extracted in 1969 by Hassanali-Walji *et al.*[39-40]



Barakol Anhydrobarakol Anhydrobarakol hydrochloride

Figure 2.7 Chemical structures of barakol, anhydrobarakol and anhydrobarakol hydrochloride[40]

Barakol consists of a chromone hemiacetal therefore barakol is unstable even in ambient condition due to a hemiacetal group easily protonated, and then loses water from its molecule to become anhydrobarakol. Anhydrobarakol is the methylene quinone derivative; it decomposes at 165°C. In hydroxylic solvents or aqueous solutions, anhydrobarakol can be reversed to barakol. Barakol is very rapidly degraded by base. In acidic conditions, barakol and anhydrobarakol can be converted to a relatively stable anhydrobarakol salt, for example anhydrobarakol bromide[39] and anhydrobarakol chloride[40]. They are stable at room temperature and in dried condition.