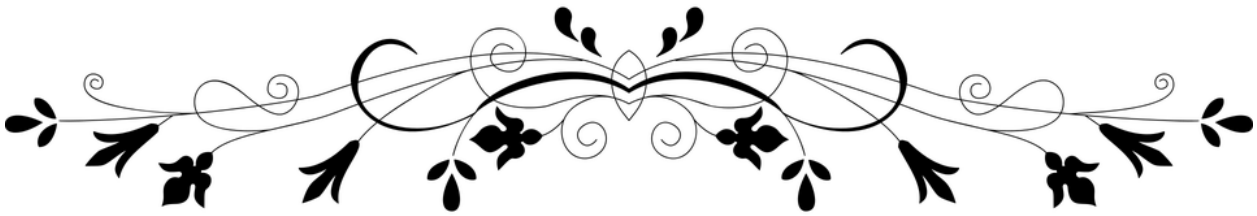

CHAPTER 1

Introduction

1. Introduction

1.1 Hydrogel

The term hydrogel was first reported in the literature in 1894 to describe colloidal gel[1]. Hydrogels can be defined as a three-dimensional network of polymeric chains formed by crosslinking via chemical or physical bonds. Chemical bonding in the hydrogel mainly involves the formation of covalent bonds, whereas physical bonding involves weak interactions such as hydrogen bonding and Vanderwaal forces. The characteristic of hydrogel is its ability to absorb water or biological fluids without dissolving in the liquid. Its three-dimensional network provides stability to the hydrogel in fluid and prevents it from dissolution. Due to its ability to disperse in water and exhibit viscoelastic behavior, hydrogels are considered colloidal systems. This behavior arises due to the incorporation of solvent in the polymeric chains and its chemical nature. Its network possesses two types of phases, solid and liquid. The solid phase includes polymers used to design hydrogel, and the liquid phase accounts for biological fluid or water incorporated in the three- dimensional networks. Its water holding capacity is governed by various factors such as the extent of crosslinking, chemical properties of polymers, and its density [2].

The swelling behavior of hydrogel depends on hydrophilic functional groups such as amine, carboxylic, hydroxyl, etc. The aqueous stability of such networks is due to the formation of a crosslink between the polymer chains. The swelling mechanism of the hydrogel is regulated by the presence of pore-size in the network. The polymeric network of the hydrogel can be classified into three categories- nonporous, microporous, and super porous. Nonporous hydrogel has very few tiny size (nm range) pores, and water diffusion is the primary mechanism responsible for its swelling. On the other hand, mesoporous

hydrogels have abundant pores, ranging from few microns to 100 microns, and swelling occurs due to diffusion and leaching of water molecules. The super porous hydrogel, on the other side, possesses abundant large size (greater than 100 microns) pores, allowing rapid uptake of water molecules and, therefore very high swelling [1].

1.2 Properties of hydrogels

1.2.1 Swelling –Hydrogels are considered polymeric networks are possessing water in their network. The water content of the hydrogel network acts as a filter for the entry of solute molecules to its network. The nature of the hydrogel polymer network plays a vital role in holding water molecules. Thus polymer network works as a matrix for water molecules. The passage of nutrients and cellular products through its network depends on the water content of the hydrogel. The water content property of hydrogel can be classified into primary bound, secondary bound, and total bound water. Primary bound water refers to the entry of initial water molecules into the dry hydrogel. The primary bound water of hydrogel occurs due to the hydration of the polar hydrophilic group. Upon complete hydration of polar hydrophilic group of hydrogel, swelling of the network occurs and results in the interaction of hydrophobic-water interactions, known as secondary bound water. The total water content of hydrogel is represented by the summation of primary bound water and secondary bound water. After saturation of polar groups and hydrophobic segment, the network acquires more water molecules due to the osmotic force created by infinite dilution. The covalent crosslinking and physical crosslinking obstruct the additional swelling and generate elastic network retraction force, resulting in swelling equilibrium. This additional swelling allows the movement of water molecules into pores, voids, or space between polymer chains of hydrogel, termed as bulk water or free water. Upon swelling, the polymer network may degrade. The

degradation of the polymeric network upon swelling depends on the nature of crosslinks between polymer chains[3].

1.2.2 Porosity-During the synthesis of hydrogel, phase separation occurs and results in the formation of pores in the hydrogel. These pores are mostly disconnected, curved and twisted, giving rise to the tortuosity in the hydrogels. The tortuosity of hydrogel is governed by pore size distribution, average pore size, and pores interconnections. The pore size of the hydrogel depends on the extent of the chemical cross-links in the polymer chains, the extent of the physical entanglements of the polymer chains, and the overall charge of the polyelectrolyte hydrogel. These pores give rise to the porosity in the hydrogels. The porosity of a hydrogel can be expressed as a void cavity inside the bulk material. Therefore, it is essential to control the porosity of the hydrogel for designing various devices such as release/loading of macromolecules and cell migration through hydrogel-based devices [3].

1.2.3 Mechanical-Generally, hydrogel displays insufficient mechanical properties. To improve its mechanical properties, developing a more complex hydrogel structure and hydrogel composite has been suggested [4]. Depending upon the complexity of the structure, the mechanical properties of the hydrogel can be tuned as per the end-use application. Generally, gel with higher stiffness can be obtained by increasing the extent of crosslinking, whereas lower stiffness can be obtained by heating the gel material. Further, it is important to note that the young modulus of hydrogel is dependent upon water content and gel matrix[3]. For instance, low or intermediate concentration polymer solutions without crosslinking show linear relation between shear stress and rate of shear. In contrast, crosslinked polymer chains and its network exhibit viscoelastic flow behavior[5]. This viscoelastic behavior can be understood by hydrogel stress relaxation studies[6].

1.3 Synthesis of hydrogel

Hydrogels can be prepared by either physical crosslinking or chemical crosslinking.

1.3.1 Physical crosslinked hydrogel

Physical crosslinking occurs due to the generation of physical crosslinks between polymer chains. Physical crosslinking occurs through different routes such as hydrogen bonding, ionic interactions, and coacervation. For example, the formation of a complex between acrylic acid and methacrylic acid with polyethylene glycol occurs through physical crosslinking via the formation of hydrogen bonding. In this complex, hydrogen bonding formed between the carboxylic group of polymethacrylic acid/ polyacrylic acid and PEG oxygen. Hydrogel formation through ionic interaction takes place in alginate gels by calcium [5]. At the same time, the polyphosphazene-based hydrogel microsphere was developed by the coacervation method[7].

1.3.2 Chemical cross-linked hydrogel

In chemical crosslinking, the formation of a new covalent bond takes place between polymer chains. The most common chemical methods used to prepare hydrogels are crosslinking polymer chains, monomer grafting, and chemical crosslinking agents. During hydrogel development through polymer precursors or polymerization of monomers, the formation of a covalent bond takes place. The most versatile method used to prepare hydrogels involves polymerization in the presence of crosslinkers. The crosslinkers are bifunctional or multifunctional chemical molecules, which allow linking between two monomers. Crosslinking of natural and synthetic polymer involves the reaction between functional group of natural/synthetic polymer with functional group of crosslinker molecules [8]. The common crosslinkers used are diisocyanates, formaldehyde, epoxy compound, and glutaraldehyde. Glutaraldehyde possesses some

advantages, such as low cost and quick reactivity. Example of natural crosslinkers includes proanthocyanidin and genipin[9].

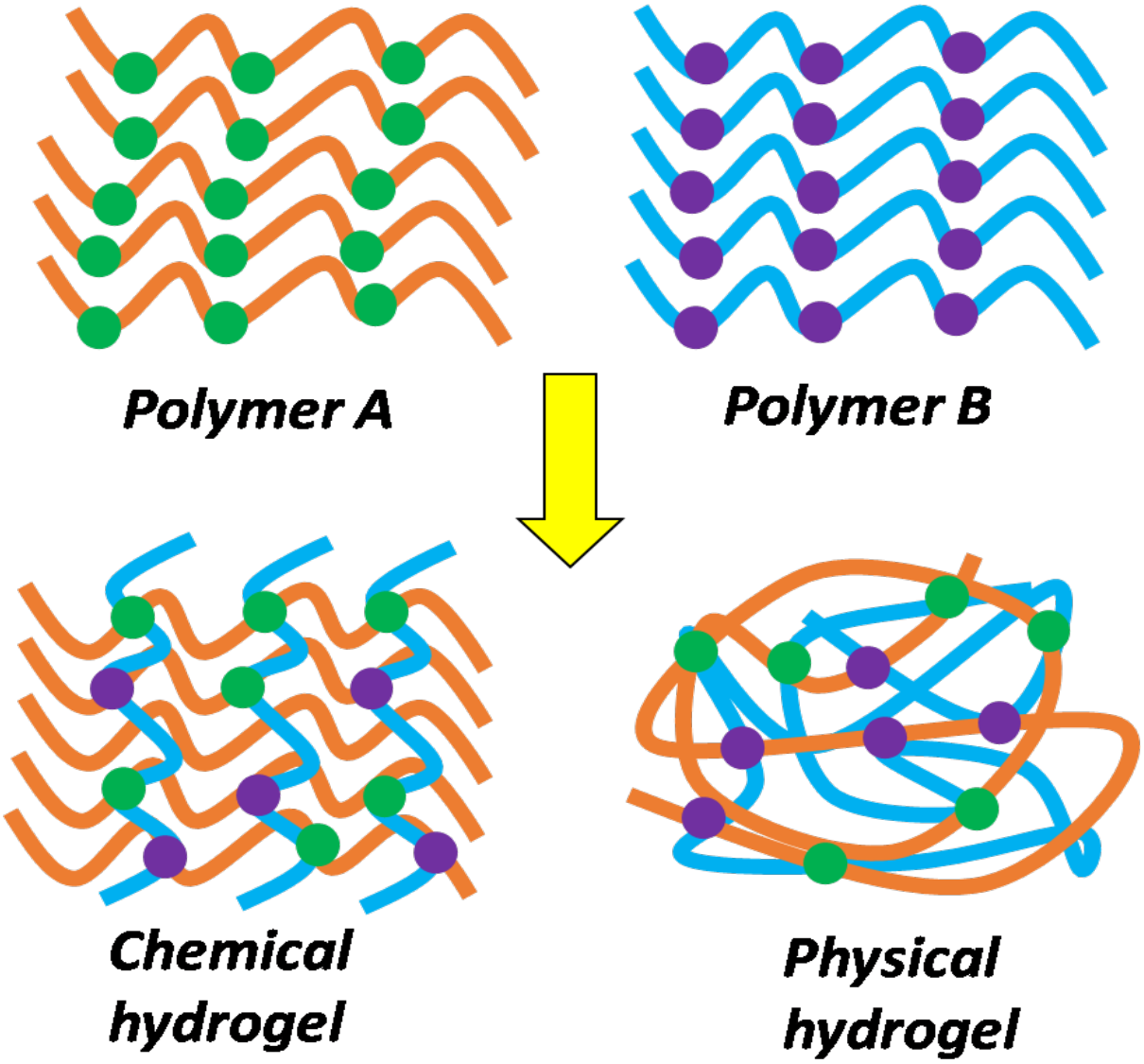

Figure 1.1- Physical and Chemical hydrogel network formation using polymer A, polymer B (Green and blue dots represents polar groups of polymer A and polymer B respectively.)

Figure 1.1 explains interaction between the two polymers during physical or chemical synthesis. On chemical hydrogel formation both polymers are crosslinked through uniform and controlled crosslinking, as a result mechanically stable network is formed [10]. On the other hand, physical crosslinking results in porous network formation via crystallite formation [11].

1.4 Classification of hydrogel-

Hydrogels can be classified based on specific features such as polymeric composition, nature of the polymeric matrix, crosslinking, biodegradability, electrical charge, stimulus responsiveness, and the physical appearance of the hydrogel.

1.4.1 Polymer composition- Hydrogels can be developed from a homopolymer, copolymer, or multi-component polymers, composed of two different independent polymers crosslinked to generate a hydrogel network.

1.4.2 Nature of polymer matrix-- Hydrogels can be prepared from synthetic polymers, a natural polymer, or semisynthetic polymer. It can also be designed by a combination of natural and synthetic polymer. Such a type of hydrogel system is called hybrid hydrogel.

1.4.3 Cross-linking- Hydrogel can be fabricated by either physical crosslinking or chemical crosslinking. Chemical crosslinking involves the use of chemical crosslinking agents resulting in the formation of permanent junctions between the polymer chains.

1.4.4 Biodegradability-To develop a biodegradable hydrogels system, biodegradable polymers are used. Generally, naturally derived polymers are used to develop biodegradable hydrogel. Although, some synthetic polymers also exhibit biodegradable characteristics and are used to create a biodegradable hydrogel system.

1.4.5 Electric charge-Hydrogel may be ionic, neutral, or amphiphilic. The presence of electric charge on the hydrogel may influence its water holding capacity.

1.4.6 Stimulus responsiveness-Stimulus-sensitive hydrogel shows responsiveness according to change in external stimuli such as pH, temperature, light, and magnetic field. This stimulus produces a change in their integrated hydrogel network.

1.4.7 Physical appearance of hydrogel-The physical appearance of hydrogel depends upon functionality, polymerization, and its application. The hydrogel may be used in coating, microparticle, nanoparticle, and films[2].

1.5 Applications of hydrogels

1.5.1 Hydrogel for tissue engineering application

When an organ partially or as a whole becomes non-functional, then treatment is required to restore or repair the function of tissue with an artificial substitute. The restoration of lost function of tissue is achieved by various approaches known as tissue engineering. The artificial substitute used in tissue engineering to repair the damaged organ or tissue is known as a scaffold. Hydrogels have been used substantially as a matrice for tissue engineering. Hydrogel-based scaffold having pores may be used to load cells, and it can be degraded naturally. The porous nature of hydrogel can be beneficial for the growth of cells over their surface. Thus hydrogel can be used to design scaffolds to treat different types of damaged tissue. The major advantages of hydrogel in tissue engineering include biocompatibility, injectability, insertion of cell adhesion molecule, protection of cell and fragile drugs. The significant disadvantages of hydrogels in tissue engineering include weak mechanical property, difficulty in handling, and sterilization[12].

1.5.2 Hydrogel for wound healing

Since hydrogels exhibit some remarkable properties such as wound exudates absorber, non-sticky behavior for newly formed tissue, permeation of oxygen to the wound site,

pain reduction at the wound site, and quick healing, these are best suited for the developing wound healing dressings, for instance. NuGel and aquagel[13]

1.5.3 Hydrogel for sensing

Hydrogels are used in the fabrication of the sensor as a coating material of its part. Coating of the sensor by hydrogel reduces its interaction with cells or biomolecules. Due to the porous and hydrophilic nature of the hydrogel, it allows the permeation of the analyte through its matrix. Although, it restricts the permeation of more giant molecules such as proteins into their network. The restriction of larger molecules is also achieved by a higher degree of cross-linking. Besides this, hydrogels can be used as a matrix for the immobilization of biosensing elements. The essential step in developing a biosensor is the immobilization of receptors in a native configuration so that it can react with the specific analyte to get accurate sensitivity and selectivity. Thus, the sensitivity and sensing characteristics of the sensor are governed by the status of immobilized sensing molecules. The excellent environment of hydrogel facilitates the maintenance of the structure of different biomolecules. Since hydrogel can be easily tailored for such applications, it can be designed for other analytes such as nucleic acid, carbohydrates, ions, and proteins. The hydrogel-based sensor can be used as the recognition element due to its interaction with the analyte, through the change in volume, according to target molecules[14].

1.5.4 Hydrogel for contact lens

Hydrogel-based contact lens made from NVP or HEMA display required oxygen permeability and can easily cover the cornea. PHEMA based hydrogel contact lenses contain 38-40 % water in a hydrated state. To fabricate such contact lenses, hydrogel must be biocompatible, hydrophilic, oxygen permeable, proper refractive index (1.45-

1.46), stable, luminous transmittance, and sufficient mechanical strength. Nowadays, silicon-based hydrogel contact lenses are used because of their high oxygen permeability[8].

1.5.5 Diagnostic and imaging

Due to significant water-content, fluidic transport behavior, and biocompatibility, the hydrogel can be used as a contrasting agent in medical imaging. Hydrogel based on PMA can be used as pH sensors in magnetic resonance imaging (MRI) without using paramagnetic material. Since the optical and electronic property of different noble-metal nanoparticles such as gold and silver depends on their size and morphology, their incorporation in the hydrogel system would further improve the contrast and consistency of images. For example, poly-dentate chelating ligands cross-linked by polyacrylamide nanogels as scaffolds are used for PET imaging. Although imaging quality from such nanogels is insufficient and further needs improvement[8].

1.5.6 Actuators

Actuators are mainly developed using metal-based materials for various applications. Although, these materials are not suitable for the fabrication of soft robots for biomedical applications. To address such shortcomings, hydrogel based actuators are used for the fabrication because they exhibit a higher degree of freedom in movement. The use of hydrogel actuators is essential for handling biomaterials or different types of tissue. Although, such hydrogels should have the adequate mechanical strength to handle cyclic loading and deformation. For example, santaniello et al. has developed a polyelectrolyte matrix embedded with cellulose nanocrystal. Due to the incorporation of cellulose nanocrystal, the mechanical property and sensitivity of hydrogel for the electric field have

been improved. This valve shaped hydrogel exhibited electro-responsive flow control [15].

1.5.7 Hydrogel for drug delivery

The hydrogel can hold up to 20% water of its weight without losing its three-dimensional integrity [12]. Based on this property, a drug-loaded hydrogel can be used as a drug-releasing device[16]and can be used for drug delivery applications. The gastrointestinal tract is considered the most common route for the delivery of drugs. Because the gastrointestinal tract provides a high surface area for systemic absorption and hydrogel-based drug delivery matrices can release drugs to a particular site in the tract. Patel and Amiji have reported their work to treat Helicobacter pylori in gastric ulcers using a hydrogel-based device. To accomplish this task, they have developed Chitosan-PEO based pH-sensitive hydrogel system [17]. Similarly, an intestine-targeted insulin delivery system was developed by Lowman. The objective of this oral insulin delivery system was to protect it from the harsh acidic medium of the stomach and to release the drug into the small intestine. They have developed microparticles, a crosslinked copolymer network of PMMA with grafted polyethylene glycol to release insulin. This formulation was further evaluated using an in-vivo study in healthy and diabetic rats for 8 hours to get information about the hypoglycemic effect. It is interesting to know that a significant outcome was observed without using protease inhibitors and absorption enhancers [18]. Since the release of drugs from hydrogel involves various physical, chemical, and biological interactions. Therefore, the theoretical prediction of drug release pattern from hydrogel is complex. The most general and accepted model used to predict the drug release profile from hydrogel is the RitgerPeppas model. This model can be presented by following equation[19]-

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t = drug release from hydrogel after time t

M_∞=Total drug release from hydrogel

k=kinetic constant, n=diffusional exponent

We have used "Korsmeyer Peppas diffusion model" in the thesis and provides the best fit to our experimental data due to which it was chosen. Besides, the KorsmeyerPeppas model, allows us to simultaneously collect information about drug release kinetics and mechanism of drug release, at the same time. This model is based on the non- linear fitting approach. Therefore, maximum experimental data of the drug release, fitted to this model. Further, it is a time efficient and precise method to know diffusion data from drug carrier [20]. In this model, "n" represents drug release mechanism of hydrogel. If the value of n is less than 0.5, then release mechanism is said to follow Fickian release or diffusion controlled release.If the value of "n" is between 0.5 and 1, then release mechanism is said to follow non-Fickian release or anomalous controlled release. While, if the value of "n" is greater than 1, then release mechanism is said to follow case 2 or relaxation controlled release [21].

Figure 1.2- Schematic representation showing biomedical applications of hydrogels