

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



## Hydrogel Biomaterials

Alpesh Patel and Kibret Mequanint

*Department of Chemical and Biochemical Engineering,  
University of Western Ontario, London Ontario,  
Canada*

### 1. Introduction

A staggering number of medical devices, diagnostic and therapeutic products that are designed to improve the health of mankind have exploited biomaterials as platform technologies (Peppas et al., 2006). Defined as natural or synthetic materials (other than drugs) to treat, augment, or replace any tissues, organ, or function of living tissues, biomaterials design requires both materials and biological considerations. In addition to the mechanical requirements, biomaterials have to accomplish some specific requirements, such as non-toxicity, desired functionality, sterilizability and biocompatibility (Rosiak & Yoshii, 1999). Despite the widespread use of biomaterials in medicine, most biomaterials do not provide all of the desired requirements to interact with biological systems. Therefore, there is a significant progress to redesign current biomaterials or to develop new materials in order to overcome limitations associated with fulfilling the above-mentioned requirements. Although the term biomaterial includes metals and ceramics, polymers account for the vast majority. In this last group, hydrogels, having considerable biocompatibility and similarity with tissue components of the body, have demonstrated great potential as one of the most promising groups of biomaterials (Rosiak & Yoshii, 1999; Rogero et al., 2003).

Hydrogels are three-dimensional (3D) materials with the ability to absorb large amounts of water while maintaining their dimensional stability. The 3D integrity of hydrogels in their swollen state is maintained either by physical or chemical crosslinking. Lower interfacial tension, soft and tissue-like physical properties, higher permeability to undersized molecules and release of entrapped molecules in a controlled manner made hydrogels to be explored in different biomedical fields (Yaszemski et al., 2004; Slaughter, 2009). In the absence of crosslinking points, hydrophilic linear polymer chains dissolve in water due to the thermodynamic compatibility of the polymer chains and water. However, in the presence of crosslinking points, solubility is counter-balanced by the retractive force of elasticity, induced by crosslinking points of the network. Swelling reaches at an equilibrium point as these forces becomes equal (Peppas et al., 2000). The amount of water absorbed in hydrogels is related to the presence of specific groups such as  $-\text{COOH}$ ,  $-\text{OH}$ ,  $-\text{CONH}_2$ ,  $-\text{CONH}-$ , and  $-\text{SO}_3\text{H}$ . Capillary effect and osmotic pressure are other variables that also influence the equilibrium water uptake of hydrogels (Dergunov & Mun, 2009).

The presence of chemical or physical crosslinking points within the network maintains the three-dimensional integrity of hydrogels in their swollen state. In chemically crosslinked hydrogels, the linear polymer chains are covalently bonded with each other via crosslinking

agents. Their usage is limited as the resulting network cannot be reshaped and/or resized since the polymer is no longer soluble in solvents and heating to melt-process can only degrade the polymer once crosslinking takes place. Moreover, the crosslinking agents applied to develop strong hydrogel network systems are mainly toxic. Thus, any unreacted crosslinking agents have to be leached out before the final application. However, partially reacted toxic crosslinking agents have no possibility to be completely leached out. In contrast, physically crosslinked hydrogels possess physical junction domains associated with chain entanglements, hydrophobic interaction, hydrogen bonding, crystallinity, and/or ionic complexation (Park & Bae 2002). The presence of these reversible crosslinking points allows solvent casting and/or thermal processing. The interest for physically crosslinked hydrogel is obvious since the use of crosslinking agents is avoided and they are beneficial for post-process bulk modification and ease of fabrication (Hennink & van Nostrum 2002; Li et al., 2002; Adams et al., 2003; Kubo et al., 2005; Liu et al., 2009). Hydrophobic – hydrophilic block copolymers are one of the well-explored and applied physically crosslinked polymers for various biomedical applications. The major disadvantage of physically crosslinked hydrogels, however, is their weak mechanical properties in the swollen state. This can be improved by using polyurethane as a hydrophobic segment into hydrophobic-hydrophilic block copolymers. Due to the excellent mechanical properties of polyurethanes (Lamba et al., 1998), hydrogels based on their chemistry are appealing for biomedical applications. Polyurethane-based hydrogels can form strongly hydrogen bonded structures, allowing linear polymer systems to be designed with tunable swelling and mechanical properties. Thus, along with the hydrophobic interaction and chain entanglements, the presence of strong H-bonding between the ether/ester and urethane groups into polyurethane can help to improve mechanical properties (Lamba et al., 1998; Mequanint et al., 2006). Following the pioneering work of Wichtl (de Groot et al., 2003) on crosslinked PHEMA hydrogels as contact lenses, hydrogels have been of great interest as potential biomaterial for cell encapsulation, drug delivery system, contact lenses, wound dressing, immunoisolation, tissue engineering scaffolds, soft tissue replacement and other related applications (Hoffman 2002; Kashyap et al., 2005).

## 2. Classifications of hydrogels

Depending on the preparation methods, ionic charges, sources, nature of swelling with changes in the environment, rate of biodegradation or the nature of crosslinking, hydrogels can be classified in several ways. A detailed classification of hydrogels is presented in Figure 1 (Dumitriu, 2002; Hin, 2004; Ratner et al., 2004). Among all, one of the important classifications is based on their crosslinking nature (Figure 1). The network stability of hydrogels in their swollen state is due to the presence of either chemical or physical crosslinking. Chemically crosslinked hydrogels are also known as thermosetting hydrogels or permanent gels. They cannot be dissolved in any solvents unless the covalent crosslink points are cleaved. Moreover, they cannot be reshaped through heat melting. They can be prepared using any of these methods:

- Copolymerizing hydrophilic monomers with crosslinkers.
- Crosslinking of water-soluble polymer segments with di and/or multi functional crosslinkers or using irradiation method (UV, microwave,  $\gamma$ -irradiation and electron beam).

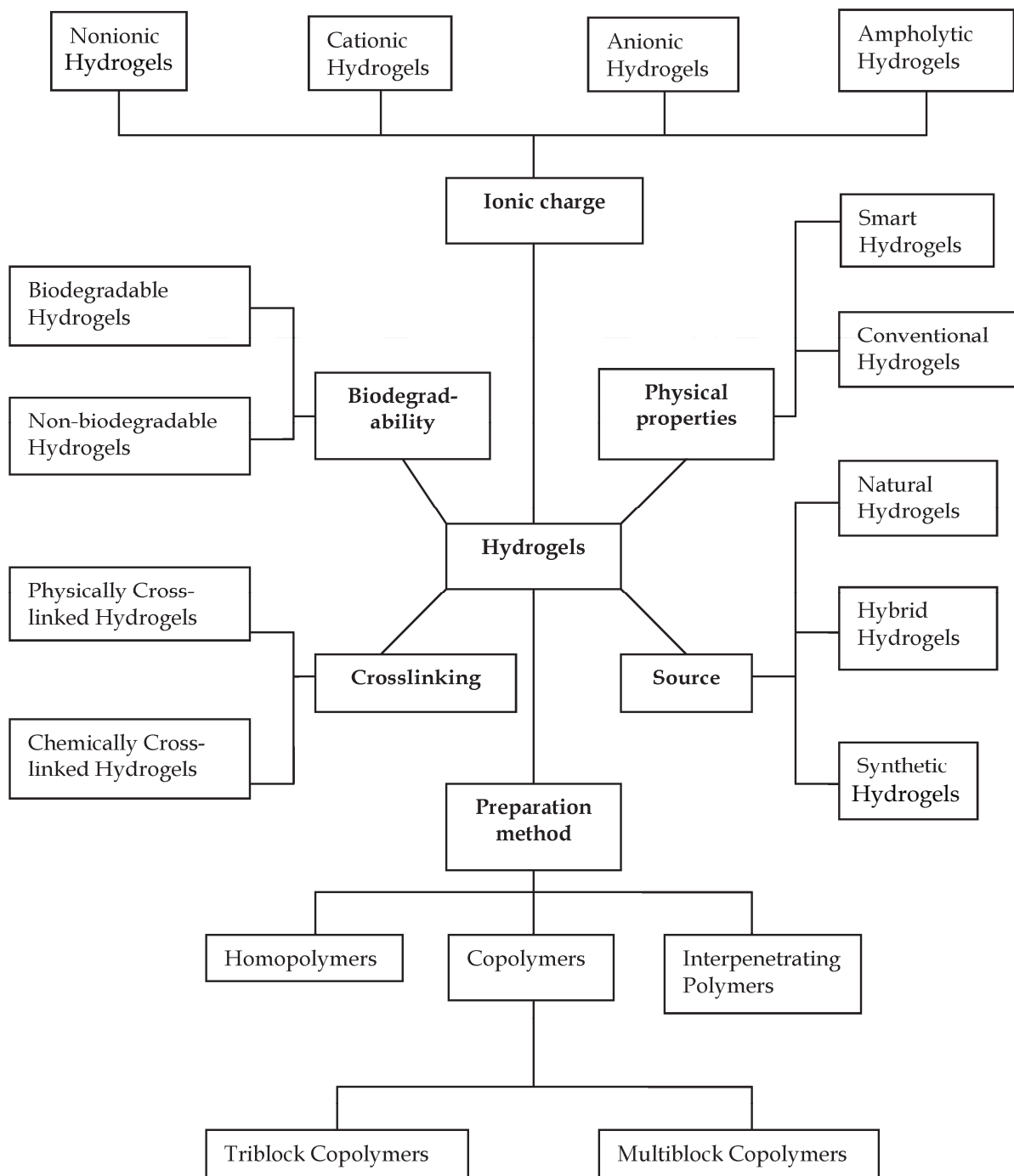


Fig. 1. Classifications of hydrogels.

The utility of chemically crosslinked hydrogels is often limited by the lack of processibility and post-process modifications. Because of this, shaping is carried out along with their polymerization reaction step. Moreover the crosslinking agents used to prepare hydrogels are highly toxic and the residues must be completely removed before their use as biomaterials. Physically crosslinked hydrogels, on the other hand, maintain their physical stability due to the presence of reversible physical junction domains associated with hydrogen bonding, hydrophobic interaction, chain entanglements, crystallinity, and/or ionic complexation (Bae et al., 2000; Qu et al., 2000; Park & Bae 2002). Physically crosslinked

hydrogels are also known as thermoplastic hydrogels or temporary gels. Swelling of these hydrogels is mostly dependent on the thermodynamic parameters such as temperature, pH, salt type and/or ionic strength. Changes in such parameters may increase or decrease their swelling. The presence of reversible crosslinking points in physically crosslinked hydrogels allows solvent casting and/or thermal processing. In the preparation of these hydrogels, the use of toxic crosslinkers can also be avoided. Physically crosslinked hydrogels possess higher compressive strength compared with the corresponding chemically crosslinked hydrogels since the mechanical load can be more uniformly distributed through the crystallites of the three-dimensional structure (Devine & Higginbotham 2003).

### 2.1 Stimuli responsive hydrogels

Stimuli responsive hydrogels are defined as hydrogels that undergo relatively large and abrupt changes in their swelling behavior, network structure, permeability and/or mechanical strength in response to small environmental changes. Stimuli responsive hydrogels are also called intelligent, smart, or environmentally sensitive hydrogels (Peppas et al., 2000; Gil & Hudson 2004). Stimuli responsive hydrogels could be further classified as either physical or chemical stimuli responsive hydrogels as shown in Figure 2.

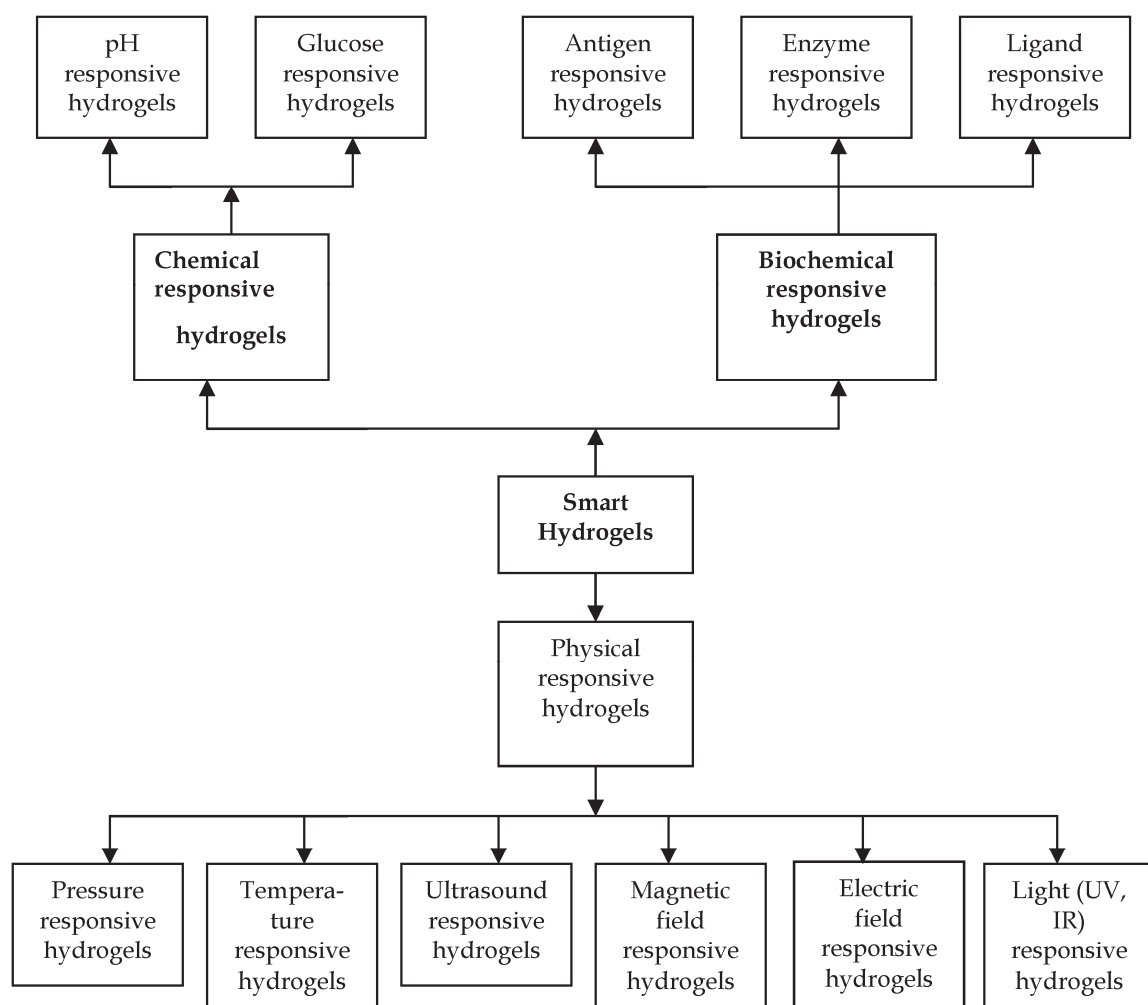


Fig. 2. Classifications of smart hydrogels.

Chemical stimuli, such as pH, ionic factors and chemical agents, will change the interactions between polymer chains or between polymer chains and solvent at the molecular level. The physical stimuli, such as temperature, electric or magnetic fields, and mechanical stress, will affect the level of various energy sources and alter molecular interactions at critical onset points. Some systems have been developed to combine two stimuli-responsive mechanisms into one polymer system, in the so-called dual responsive polymer systems. Polyacrylic acid-co-polyvinyl sulfonic acid is an example of dual responsive polymer system (Kim et al., 2004). Recently, biochemical stimuli have been considered as another category, which involves the responses to antigen, enzyme, ligand, and other biochemical agents (Peppas, et al. 2000; Gil & Hudson 2004). Thus stimuli-responsive hydrogels are appealing biomaterials for pharmaceutical, biotechnological and biomedical applications (Kashyap et al., 2004).

## 2.2 pH responsive hydrogels

pH responsive hydrogels are made of polymeric backbones with ionic pendant groups that can accept and/or donate protons in response to an environmental pH change (Bushetti et al., 2009). As the environmental pH changes, the degree of ionization in pH responsive hydrogel is dramatically changed at specific pH known as pKa or pKb. This rapid change in the net charge of ionized pendant groups causes abrupt volume transition by generating electrostatic repulsive forces between ionized groups, which creates large osmotic swelling force. There are two types of pH responsive hydrogels: anionic and cationic hydrogels. In anionic hydrogels having pendant groups such as carboxylic (Ende & Peppas 1996; Ying et al., 1998; Jabbari & Nozari 1999; Jianqi & Lixia 2002; Wang et al. 2006) or sulfonic acid, deprotonation occurs when the environmental pH is above the pKa leading to the ionization of the pendant groups. This, in turn, increases swelling of the hydrogel. On the other hand, in cationic hydrogels containing pendant groups such as amine groups (Baker et al., 1992), ionization takes place below the pKb and this increases the swelling due to an increase in electrostatic repulsions (Gupta et al., 2002). Two major factors control the degree of swelling of ionic hydrogels. The first factor is the properties of the polymers such as ionic charge, concentration and pKa or pKb of the ionizable groups, degree of ionization, crosslink density as well as hydrophilicity or hydrophobicity. The second factor is the properties of the swelling medium like pH, ionic strength and the counterion and its valence (Gupta et al., 2002). Polyvinyl sulfonic acid (PVSA) (Kim et al., 2005), polymethacrylic acid (PMAA) (Eichenbaum et al., 1998; Kozlovskaya et al., 2006) polydiethylaminoethyl methacrylate (PDEAEMA) (Vamvakaki et al., 2006) and polydimethylaminoethyl methacrylate (PDMAEMA) (Sen & Sari, 2005; Bossard et al., 2006) and their copolymers are other examples of pH responsive hydrogels.

## 2.3 Temperature responsive hydrogels

Temperature responsive hydrogels have gained considerable attention in the biomedical field. Numerous researchers studied various applications of these hydrogels, in the area of smart drug delivery system, injectable scaffolds, biosensors and intelligent cell culture dishes (Peppas et al., 2000; Schmaljohann et al., 2003; He et al., 2008). Temperature responsive hydrogels can be classified as positive or negative temperature responsive systems. Physically crosslinked thermo sensitive hydrogels may undergo sol-gel phase transitions instead of volume change at a critical solution temperature (Peppas et al., 2000; Kashyap et al., 2004). Positive temperature responsive hydrogels show phase transition at critical temperature called the upper critical solution temperature (UCST). Hydrogels made

from polymers with UCST shrink when cooled below their UCST. Negative temperature responsive hydrogels have a lower critical solution temperature (LCST). These hydrogels shrink upon heating above their LCST. Chemically crosslinked thermo sensitive hydrogels undergo volume change rather than sol-gel transitions. Certain molecular interactions, such as hydrophobic associations and hydrogen bonds play vital role in the abrupt volume change of these hydrogels at the critical solution temperature (CST). In the swollen state, water molecules form hydrogen bonds with polar groups of polymer backbone within the hydrogels and organize around hydrophobic groups as iceberg water. At the CST, hydrogen bonding between the polymer and water, compared to polymer-polymer and water-water interactions, becomes unfavorable. This forces the quick dehydration of the system and water is released out of the hydrogel with a large gain in entropy, resulting in shrinkage of the polymeric structure (Kopecek, 2003; Ruel-Gariepy & Leroux 2004). The mostly studied temperature responsive hydrogels are methylcellulose (Stabenfeldt et al. 2006), hydroxypropyl methylcellulose (Vinatier et al., 2005), chitosan (Zan et al., 2006), *N*-isopropylacrylamide (NIPAAm) based copolymers (Lu et al., 2000; Kim et al., 2002; Schmaljohann, 2005; Lee et al., 2006; Qiao et al., 2006) and other *N*-alkylacrylamide polymers (Hirokawa & Tanaka, 1984), poly(vinyl methyl ether) (PVME) (Kabra et al., 1992; Arndt, Schmidt et al. 2001; Theiss et al. 2004), poly(*N*-vinylisobutyramide) (PNVIBA) (Akashi et al., 1996; Kunugi et al., 1997; Suwa et al., 1997; Suwa et al., 1997), poly(ethylene oxide-*b*-propylene oxide-*b*-ethylene oxide) (PEO-PPO-PEO) (Bohorquez et al., 1999; Song, Lee et al., 2000), and poly(ethylene oxide)/(D,L-lactic acid-co-glycolic acid) (PEO-PLLA-PLGA)(Jeong et al., 1997) copolymers. Poly(*N*-isopropylacrylamide) (PNIPAAm) is the most popular temperature-responsive polymer since it exhibits a sharp phase transition in water at 34.3°C which is close to physiological temperature (Peppas et al., 2000). Its LCST can be controlled by copolymerizing with other monomers. The LCST increases with the addition of hydrophilic monomers whereas it decreases with the incorporation of hydrophobic monomers. Grafting of hydrophilic or hydrophobic monomers does not show any significant changes in LCST (Ruel-Gariepy & Leroux, 2004).

#### 2.4 Glucose responsive hydrogels

For the treatment of diabetes, desirable insulin delivery hydrogel systems could be developed having glucose-sensing carrier to trigger the release of required amounts of insulin. Glucose sensitive hydrogels have been attractive for this particular application. Cationic hydrogels as a carrier for insulin and glucose oxidase mixture are the most extensively studied glucose sensor systems (Podual et al., 2000; Podual et al., 2000; Traitel et al., 2000; Brahim et al., 2002). In the presence of oxygen, glucose oxidase converts glucose to gluconic acid and reduces the local pH; which increases the swelling of cationic hydrogels and releases insulin. To improve controlled loading of insulin, glucose oxidase has been covalently tethered on the hydrogel system that reduces its fast diffusion out of the system (Kang & Bae 2003). Other mechanisms including the use of concanavalin-A as a crosslinker (Obaidat & Park 1996), use of phenylboronic acid (Shiino et al., 1995) or glucose dehydrogenase (Kashyap et al., 2004) as a biosensor have been also investigated to fabricate glucose responsive hydrogels.

#### 2.5 Protein-based hydrogels

Protein-based hydrogels have been studied for drug delivery and tissue engineering applications (Wang et al., 1999; Xu et al., 2005). These protein-based hydrogels are precisely

designed with defined compositions, sequences, stereochemistry, and molecular weights using recombinant DNA technology. Coiled-coil is an attractive approach for protein-based hydrogels. The hydrophobic amino acid residues of coiled-coil proteins are used as physical crosslinkers in protein-based polymer hydrogels. Tri-block copolymers with coiled-coil domains at the end and water-soluble polypeptide domain at the centre have been designed as physically crosslinked protein-based hydrogels (Wright & Conticello 2002; Wright et al., 2002). Consequently, temperature and/or pH-responsiveness may be achieved by manipulating the amino acid sequences of the coiled-coil domains (Kopecek, 2003; Xu et al., 2005). Addition of RGD sequence within the hydrophilic polypeptide sequence also improves cell interactions. Moreover, coiled-coil proteins are used as crosslinkers with water soluble linear synthetic polymers to prepare 3D structure of hydrogels (Wang et al., 1999).

### **2.6 Antigen-responsive hydrogels**

Antigen-responsive hydrogels have been designed to deliver biomolecules at a specific targeted site (Miyata et al., 1999; Lu et al., 2003). In these hydrogels, antigens are grafted on hydrophilic polymeric backbones. They can also be mixed with antibody-grafted crosslinked hydrophilic polymeric backbones. In the absence of a free antigen, the hydrogel structure shrinks due to the intra-chain antigen-antibody binding in the polymer network. Specific molecular recognition is a remarkable feature of the antigen-sensitive hydrogels that made them useful biomaterials to fabricate an antigen sensing device for biomolecules, protein or drug delivery at desired sites (Miyata et al., 2002).

## **3. Water in hydrogels**

Swelling behavior of hydrogel systems is an important parameter governing their applications specifically in pharmaceutical, ophthalmology and tissue engineering. The presence of water at the surface of hydrogels reduces the interfacial free energy in a physiological environment and thus improves their biological properties (Jhon & Andrade 1973). The final water content of hydrogels depends on both kinetics and thermodynamics parameters. During the swelling process, the first water molecules hydrate the most polar, hydrophilic groups, and this portion of water is called 'primary bound water'. As the hydration of polar and hydrophilic groups is completed, the network swells, and exposes hydrophobic groups, which start interacting with water through hydrophobic interaction called secondary bound water molecules. Together, primary and secondary bound water molecules are often called the total bound water (Hoffman, 2002). After the water has interacted with both hydrophilic and hydrophobic sites, the osmotic driving force of the network chains allows the network to absorb more water. This additional swelling is opposed by the presence of covalent or physical crosslinking junctions through an elastic network retraction force. Finally, the balance of the retraction force and the infinite dilution force establish an equilibrium swelling level. The additional water absorbed beyond the total bound water is defined as 'free water' or 'bulk water' (Hoffman, 2002).

### **3.1 Thermodynamics of hydrogel swelling**

Hydrophilic polymer networks show high affinity to water and, in the presence of water, the polymer-water interaction is preferred to the inter-polymer chains interactions. Thus, the hydrophilic network allows large water absorption and proceeds towards infinite dilution.



However, the presence of crosslinking junctions resists the infinite dilution by the retractive force of elasticity. In the absence of ionic moieties in the polymer chains, the counter balance of these forces decides the water uptake of hydrogels. The Flory-Huggins theory can be used to calculate the thermodynamic behavior of hydrogel swelling (Flory, 1953; Peppas et al., 2000; Ratner 2004). Considering an isotropic crosslinked structure of hydrogel, the total Gibbs free energy change of the system, upon swelling, can be written as:

$$\Delta G = \Delta G_{\text{mixture}} + \Delta G_{\text{elastic}} \quad (1)$$

Where,

$\Delta G_{\text{mixture}}$  = the free energy of mixing due to water affinity of hydrophilic polymers.

$\Delta G_{\text{elastic}}$  = the elastic free energy as a result of the network expansion.

In order to express the chemical potential change of water in terms of elastic and mixing contributions at any time of swelling, differentiating equation (1) with respect to the water molecules in the system gives:

$$\mu_{\text{wh}} - \mu_{\text{pw}} = \Delta\mu_{\text{mixture}} + \Delta\mu_{\text{elastic}} \quad (2)$$

Where,

$\mu_{\text{wh}}$  = the chemical potential of water within the hydrogel.

$\mu_{\text{pw}}$  = the chemical potential of pure water.

$\Delta\mu_{\text{mixture}}$  = the change in chemical potential due to mixing.

$\Delta\mu_{\text{elastic}}$  = the change in chemical potential as a result of the network expansion.

The chemical potential change on mixing can be obtained using Flory-Huggins theory that is applied to the fundamentals of the thermodynamics of polymer solution.

### 3.1.1 Determination of $\Delta\mu_{\text{mixture}}$ –the entropy of mixing

In the absence of crosslinkages, the ideal entropy of mixing can be given by the Boltzmann relation,  $\Delta S_m = k \times \ln \Omega$ . Here  $k$  represents the Boltzmann constant and  $\Omega$  represents the probability of arrangements of polymer chains within the solvent. By considering that the polymer molecules have the same size, the Lattice Model can be used to find the possibility of such arrangements. The formation of the polymer solution can be thought to happen in two steps: disorientation of the polymer chains and mixing of the disoriented polymer with solvent. The entropy change related to both steps and the overall entropy change is given as:

$$\Delta S_m = -k(n_1 \ln v_1 + n_2 \ln v_2) \quad (3)$$

Where,

$v_1$  = volume fraction of water

$v_2$  = volume fraction of polymer

$n_1, n_2$  = moles of water and polymer respectively.

### 3.1.2 Determination of $\Delta\mu_{\text{mixture}}$ – the heat of mixing

According to the Lattice Model, three types of first neighbor contacts are possible: [1,1], [2,2] and [1,2]. The solution is prepared by having the chemical reaction in which bonds of [1,2]

types are formed at the expense of an equal number of [1,1] and [2,2] as per the following stoichiometric balance:

$$\frac{1}{2}[1,1] + \frac{1}{2}[2,2] = [1,2]$$

If  $w_{11}$ ,  $w_{22}$  and  $w_{12}$  are the energies associated with these respective bonds, the change in energy due to the formation of unlike pairs is given as:

$$\Delta w_{12} = w_{12} - \frac{1}{2}(w_{11} + w_{22})$$

The overall heat of mixing is then given as:

$$\Delta H_m = \Delta w_{12} \times p_{12} = z \Delta w_{12} x_1 n_1 v_2 \quad (4)$$

Where,

$p_{12}$  = probability that the sites adjacent to a polymer segment is occupied by a solvent molecule =  $z x_1 n_1 v_2$ .

$z$  = the lattice coordination number which equals the number of cells which are first neighbors to a given cell.

$x_1$  = the segments of water molecule.

The quantity  $z \Delta w_{12} x_1$  represents the change in the internal energy of a solvent molecule immersed in the pure polymer compared with the one surrounded by molecules of its own kind, i.e., in the pure solvent. Another parameter is introduced to define this energy difference and is called water-polymer interaction parameter ( $\chi$ ). It is the dimensionless quantity, which is defined as  $\frac{z \Delta w_{12} x_1}{kT}$ . Using this interaction parameter into the equation

(4) gives:

$$\Delta H_m = kT \chi n_1 v_2 \quad (5)$$

### 3.1.3 The chemical potential change on mixing

The Gibbs free energy of the mixing is simply given by combining equations (3) and (5). That is,

$$\Delta G_m = \Delta H_m - T \Delta S_m = kT \chi n_1 v_2 + kT (n_1 \ln v_1 + n_2 \ln v_2)$$

$$\Delta G_m = \Delta H_m - T \Delta S_m = kT (\chi n_1 v_2 + n_1 \ln v_1 + n_2 \ln v_2) \quad (6)$$

Now, in the case of hydrogels, the number  $n_2$  of polymer molecules is to be equated to zero owing to the absence of individual polymer molecules in the network structure. Thus

$$\Delta G_m = kT (\chi n_1 v_2 + n_1 \ln v_1) \quad (7)$$

Differentiation of the above equation with respect to the number water molecules,  $n_1$ , at constant temperature and pressure (bearing in mind that  $v_1$  and  $v_2$  are functions of  $n_1$ ) into the system gives,

$$\Delta\mu_{\text{mixture}} = \frac{\partial\Delta G_m}{\partial n_1} = kT(\ln v_1 + v_2 + \chi v_2^2) \quad (8)$$

### 3.1.4 Determination of $\Delta\mu_{\text{elastic}}$

The presence of crosslinks induces a retractive force as the dry hydrogel expand into the water. This retractive force can be explained by using the theories of rubber elasticity. Rubbers are materials that respond to stresses with nearly instantaneous and fully reversible deformation up to 1000% elongation. Rubbers are crosslinked networks possessing large free volume that makes them capable to respond to external stresses by rearranging the polymer chains. In the swollen state, most hydrogels satisfy this phenomenon of rubber. To derive the relationship for the chemical potential change of water during swelling, statistical thermodynamics have been used<sup>69</sup>. The expansion of hydrogel is considered to be isotropic. So the developed strain related to the expansion of structure (say  $\alpha_s$ ) can also be considered the same in all direction. The entropy change involved in expansion of hydrogels, obtained by using statistical thermodynamics and by applying the Boltzmann expression (Flory, 1953) is:

$$\Delta S_{el} = -\frac{kv_e}{2} [\alpha_x^2 + \alpha_y^2 + \alpha_z^2 - 3 - \ln(\alpha_x\alpha_y\alpha_z)] \quad (9)$$

Using  $\alpha_s = \alpha_x = \alpha_y = \alpha_z$ , for isotropic expansion, we get

$$\Delta S_{el} = -\frac{kv_e}{2} [3\alpha_s^2 - 3 - \ln(\alpha_s^3)] \quad (10)$$

The extensibility of a rubber is driven by entropic change rather than enthalpic changes. For ideal elastic behavior, the extension takes place due to the rearrangement of polymer chains and bonds are not stretched with change in length. This behavior is not true for most other materials (e.g. metals) where changes in length cause internal energy driven retractive force. For elastomeric materials, an increase in length is counter-balanced by decreasing the entropy only, which is due to the changes in the end-to-end distances of the network chains. The extensibility of hydrogels during swelling can be considered in the same way. The enthalpy change is ideally zero and practically very small in the case of swelling. By neglecting the enthalpy change during swelling, the free energy of elasticity for swelling is given as:

$$\Delta G_{\text{elastic}} = \Delta H_{\text{elastic}} - T\Delta S_{\text{elastic}} = \frac{kTv_e}{2} [3\alpha_s^2 - 3 - \ln(\alpha_s^3)] \quad (11)$$

Differentiation of the above equation with respect to the number water molecules,  $n_1$ , at constant temperature and pressure (having in mind that  $\alpha_s$  is the function of  $n_1$ ) into the system gives,

$$\frac{\partial\Delta G_{\text{elastic}}}{\partial n_1} = kTv_e V_1 \left[ v_2^{1/3} - \frac{v_2}{2} \right] \quad (12)$$

Where,

$V_1$  = molar volume of water

$v_2$  = volume fraction of unswollen polymer in swollen hydrogel

$v_e$  = effective crosslinking density =  $\frac{v_n}{V_0}$

$v_n$  = effective number of polymer chains in the network

$V_0$  = volume of unswollen polymer

This equation assumes that the network is ideal and all chains in the network are elastically active to contribute to the elastic stress. In hydrogels, free chain ends represent gel network “defects” that do not contribute to the elasticity of the network. Other network defects are chain “loops” and entanglements, which also do not contribute to the permanent network elasticity. These network imperfections such as chain entanglements, and chain ends are not taken into account. The corrected equation for these imperfections is:

$$\frac{\partial \Delta G_{el}}{\partial n_1} = kT \left( \frac{V_1}{v_a M_c} \right) \left( 1 - \frac{2M_c}{M_n} \right) \left( v_2^{1/3} - \frac{v_2}{2f} \right) \quad (13)$$

Where,

$v_a$  = specific volume of unswollen polymer

$M_c$  = the number average molecular weight between cross-link points

$M_n$  = the number average molecular weight of linear polymer chains prepared at the same conditions without crosslinking.

$f$  = functionality of crosslinking agent.

Now, the overall chemical potential change of water in swollen hydrogel is

$$\mu_{wh} - \mu_{pw} = \Delta\mu_{mixture} + \Delta\mu_{elastic}$$

$$\Delta\mu = N_A \left[ \frac{\partial \Delta G_m}{\partial n_1} + \frac{\partial \Delta G_{el}}{\partial n_1} \right]$$

$$\Delta\mu = N_A \left[ kT (\ln v_1 + v_2 + \chi v_2^2) + kT v_e V_1 \left( v_2^{1/3} - \frac{v_2}{2} \right) \right]$$

$$\Delta\mu = RT \left[ \ln v_1 + v_2 + \chi v_2^2 + v_e V_1 \left( v_2^{1/3} - \frac{v_2}{2} \right) \right] \quad (14)$$

Here,  $N_A$  is the Avogadro's number and from the definition;  $k = R/N_A$ .

At equilibrium, the chemical potential of the water within hydrogel must be the same as that of pure water. The term at the right hand side of the equation (14) should be zero at equilibrium. At the equilibrium we can write:

$$\Delta\mu = RT \left[ \ln v_1 + v_2 + \chi v_2^2 + v_e V_1 \left( v_2^{1/3} - \frac{v_2}{2} \right) \right] = 0 \quad (15)$$

$v_1$  can be eliminate in favor of  $v_2$  since  $v_1 = 1 - v_2$ . This equation is used to calculate the number average molecular weight between crosslinks:

$$\chi = -\frac{\ln(1-v_2) + v_2 + v_e v_1 \left( v_2^{1/3} - \frac{v_2}{2} \right)}{v_2^2} \quad (16)$$

### 3.2 Kinetics of hydrogel swelling

The kinetic behavior of hydrogel swelling is mainly due to diffusion and capillary rise of water into the hydrogel. Water uptake through capillary rise is much faster than the diffusion process. 1-cm rise of fluid in a narrow capillary (~100 μm) takes place in the order of milliseconds (Yui et al., 2004). The presence of small pore size (100 μm to 300 μm), good pore size distribution and extensive interconnected capillary channels in super porous hydrogel systems, make them fast swelling systems that are advantageous for specific applications such as sanitary adsorbants. Following capillary rise, diffusion of water into the polymer network takes place. The network relaxation, limited by the water-polymer interaction, plays a major role during the water diffusion process. To determine the nature of water diffusion into the hydrogels, the swelling data over the time intervals has been fitted into the Fickian diffusion equation (Ritger & Peppas 1987):

$$f = \frac{W_t}{W_\infty} = Kt^n \quad (17)$$

Where,  $f$  is the fractional water uptake at time  $t$ ,  $W_t$  and  $W_\infty$  are the mass of the hydrogel at time  $t$  and at equilibrium swelling respectively,  $K$  is a characteristic rate constant that rely on the hydrogel structure and,  $n$  is a transport number that indicates whether diffusion and/or network relaxation controls the swelling. For one-dimensional slab geometry, the swelling is diffusion controlled for  $n \leq 0.50$ , known as Fickian diffusion, where the rate of network relaxation is faster than the rate of diffusion. For  $n = 1.00$ , water transport is controlled by the rate of relaxation of the polymer network where the rate of diffusion is faster than rate of network relaxation and is known as non-Fickian diffusion. For the value of  $n$  between 0.50 and 1.00, both rates affect considerably on the swelling rate and none of their effect can be neglected. Such transport is called anomalous diffusion. For non-Fickian behavior of hydrogels, the deviation from Fickian behavior is due to the finite rates at which the polymer structure may change or reorient in response to the sorption or desorption of water molecules. In such polymers, a sorption process will be affected through the segmental motion that occurs at about the same rate or slower than the diffusion process. Thus, non-Fickian behavior is polymer structure dependant, and based on the polymer composition, wide range of relaxation times associated with structural changes can be observed. A number of mathematical models have been proposed for non-Fickian behavior of polymers (Ritger & Peppas 1987), however no single model successfully predicts all experimental observations.

For diffusion controlled swelling kinetics, the diffusion coefficient ( $D$ ) is used to describe the rate of swelling. The flux,  $J$ , of a diffusing substance through the unit area of a section can be expressed by Fick's first law (Ritger & Peppas 1987):

$$J = -D \left( \frac{\partial C}{\partial x} \right) \quad (18)$$

Where,  $\left(\frac{\partial C}{\partial x}\right)$  is the concentration gradient which is the driving force for diffusion, and  $D$  is the diffusion coefficient. The diffusion coefficient is a constant and independent of  $x$ ,  $C$ , and time,  $t$ . When the concentration gradient varies with time, the rate of change of concentration in one-dimension is given by Fick's second law (Ritger and Peppas 1987):

$$\left(\frac{\partial C}{\partial t}\right) = D \left(\frac{\partial^2 C}{\partial x^2}\right) \quad (19)$$

Several solutions for equation 19 that depend on the boundary conditions were developed by Crank (Ritger & Peppas 1987). Using the time-dependent swelling data on thin films, the following equation can be used to calculate diffusion coefficient of water considering unsteady state diffusion and using planar geometry (Ritger & Peppas 1987):

$$\frac{W_t}{W_\infty} = \left(\frac{16D}{\pi L^2}\right)^{0.50} \times t^{0.50} \quad (20)$$

Where,  $L$  is the initial section thickness and  $D$  is the diffusion coefficient of water. Thus, the slope of the plot of  $\frac{W_t}{W_\infty}$  against  $t^{0.50}$  provides the diffusion coefficient of water for a given hydrogel system. Equation 20 is a good approximation for the solution obtained when the surface concentration is constant at both sides of the film for values of  $\frac{W_t}{W_\infty}$  less than 0.6.

Thus, when fractional swelling,  $\frac{W_t}{W_\infty}$ , is linear with the square root of time, the swelling profiles fit Fick's law, allowing the determination of diffusion coefficients.

#### 4. Applications of hydrogels as biomaterials

Certain important properties of hydrogels for their applications as biomaterials can be tabulated as follows:

- Superior biocompatibility
- Good oxygen permeability
- Low protein adsorption and cell adhesion
- Aqueous surface environment to protect cells and therapeutic drugs (peptides, proteins, oligonucleotides, DNA)
- Minimal frictional irritation within the surrounding tissues upon implantation
- Soft and tissue-like physical properties
- Micro-porous structure for additional transport channels
- Ease of surface modification with specific biomolecules
- Can be injected in vivo as a solution that gels at body temperature

These properties of hydrogels made them ideal biomaterials for applications in drug delivery system, cell encapsulation, contact lenses, scaffolds for tissue engineering, biosensors, intelligent cell culture substrates, wound dressing, soft tissue replacement and many more.

#### 4.1 Hydrogels for drug delivery applications

Well-designed drug delivery systems must control solute release over time. Various biomaterials have been investigated to control drug release; however, among them, hydrogels show two distinct advantages. (i) Drugs can easily diffuse out through the hydrogels. The rate of drug release can be controlled in many ways such as by changing the crosslinking density, preparing the hydrogel with monomers of controlled hydrophilicity and/or controlling the ratio of hydrophilic to hydrophobic monomers. (ii) Compared with hydrophobic materials, hydrogels may interact less strongly with drugs; consequently, a larger fraction of active molecules of drug, especially proteins and peptides, can be released through hydrogel carriers (Silva et al., 2009).

#### 4.2 Hydrogels for cell encapsulation

Cell encapsulation technology provides a promising therapeutic modality for diabetes, hemophilia, cancer and renal failure (Orive et al., 2003; Orive et al., 2004). The selection of a suitable biomaterial as a membrane for encapsulating cells is the major challenge towards the success of cell encapsulation therapy. Biocompatibility, microporous structure and minimal surface irritation within the surrounding tissues of hydrogels attracted them for this application. They can be designed with required porosity that resists any entrance of immune cells and allows stimuli, oxygen, nutrients and/or waste transfer through the pores. Genetically modified alginates (King et al., 2003) and polyethylene oxide based hydrogels (Miura et al., 2006) have been studied as cell encapsulation systems.

#### 4.3 Hydrogels for tissue engineering scaffolds

Tissue engineering has emerged as a promising technology for the design of an ideal, responsive, living substitute with properties similar to that of the native tissue (Lee & Mooney 2001). To date, it has focused mainly on restoration, maintenance and/or improvement of the functions of bone, cartilage, tendon, ligament, skin, blood vessels and heart valves. Scaffolds play an important role in scaffold-guided in vitro tissue engineering. Scaffolds are basically 3D structural templates which support cell adhesion, migration, differentiation, proliferation and provide guidance for neo tissue formation. The chosen scaffold material should be biocompatible and reproducible without any batch-property variation with high porosity and well organized inter-connectivity (Patel et al., 2006). Hydrogels in particular emerged as useful scaffolding biomaterials as they most closely resemble the natural tissues. Moreover, an aqueous environment provided by hydrogels mimics those of cells in the body. They are porous for nutrient and waste diffusion, and as discussed before they are usually considered to be biocompatible. However, the possibility of batch to batch variation is an issue with natural hydrogels which can be overcome using biologically modified synthetic hydrogels. Both synthetic and natural hydrogels are used as scaffolds for tissue engineering in order to repair cartilage, tendon, ligament, skin, blood vessels and heart valves (Drury & Mooney 2003; Patel et al., 2006). Synthetic hydrogels focused as scaffolds are polyurethanes (PU), poly(ethylene oxide) (PEO), poly(*N*-isopropylacrylamide) (PNIPAAm), poly(vinyl alcohol) (PVA), poly(acrylic acid) (PAA) and poly(propylene fumarate-*co*-ethylene glycol) (P(PF-*co*-EG)) whereas, naturally derived hydrogels are agarose, alginate, chitosan, collagen, fibrin, gelatin, and hyaluronic acid (HA) (Peppas et al., 2006).

#### 4.4 Hydrogels for contact lens application

The cornea of the eye is a precisely formed transparent structure of protein fibers containing about 80% water and 20% formed materials making it a natural hydrogel (Merrett et al., 2009). Synthetic hydrogels have found to be suitable in contact lens applications when the refractive power of cornea is compromised. In addition to their biocompatibility and softness, inter-connected microstructures of hydrogels help oxygen diffusivity to the epithelial layer of the cornea. Certain hydrogels possess high refractive index, modulus, and transparency, required to fit for this application. Poly(HEMA) was the first hydrogel used as a contact lens in 1960 (Wichterle & Lim 1960). Since no single hydrophilic polymer structure provides all required properties, copolymers developed from a group of hydrophilic monomers like dimethylacrylamide (DMAAm), N-vinyl pyrrolidone (NVP) and methacrylic acid (MAA) and hydrophobic monomers like perfluoro polyethers (PFPE), methyl methacrylate (MMA) and silicon-containing monomers are utilized to design contact lenses (Nicolson & Vogt 2001; de Groot et al., 2003).

Moreover, hydrogels have also been studied as potential biomaterials for biosensors (Miyata et al., 2002), intelligent cell culture dish (Schmaljohann et al., 2003), wound-dressing (Sen & Avci 2005), injectable scaffolds (Stile & Healy 2001), and soft tissue replacement (Millon & Wan 2006).

#### 5. Conclusions

Hydrogels are important classes of biomaterials with attractive properties. The review presented in this chapter highlights some aspects of hydrogel properties and applications. It is expected that hydrogels will continue to play significant roles in biomedical engineering applications.

#### 6. References

- Adams, M.; Lavasanifar A. & Kwon, G. (2003). Amphiphilic block copolymers for drug delivery. *Journal of Pharmaceutical Sciences*. Vol. 92, No. 7, (July 2003), pp. 1343-1355, ISSN: 0022-3549.
- Akashi, M., Nakano, S. & Kishida, A. (1996). Synthesis of poly(N-vinylisobutyramide) from poly(N-vinylacetamide) and its thermosensitive property. *Journal of Polymer Science Part A-Polymer Chemistry*. Vol. 34, No. 2, (January 1996), pp. 301-303, ISSN: 1099-0518
- Arndt, K.; Schmidt, T. & Menge, H. (2001). Poly (vinyl methyl ether) hydrogel formed by high energy irradiation. *Macromolecular Symposia*. Vol. 164, No. 1, (February 2001), pp. 313-322.
- Bae, Y.; Huh, K.; Kim, Y. & Park, K. (2000). Biodegradable amphiphilic multiblock copolymers and their implications for biomedical applications. *Journal of Controlled Release*. Vol. 64 No.1-3 (February 2000), pp. 3-13, ISSN: 0168-3659.
- Baker, J.; Stephens, D., Blanch, H. & Prausnitz, J. (1992). Swelling Equilibria for Acrylamide-Based Polyampholyte Hydrogels. *Macromolecules*. Vol 25, No.7, (February 1992), pp. 1955-1958, ISSN 0024-9297.
- Bohorquez, M.; Koch, C., Trygstad, T. & Pandit, N. (1999). A study of the temperature-dependent micellization of pluronic F127. *Journal of Colloid and Interface Science* Vol. 216, No. 1, (August 1999), pp.34-40, ISSN:1095-7103.



- Bossard, F; Aubry, T., Gotzamanis, G. & Tsitsilianis, C. (2006). pH-Tunable rheological properties of a telechelic cationic polyelectrolyte reversible hydrogel. *Soft Matter*. Vol. 2, No. 6, (May 2006), pp. 510-516, ISSN 1292-8941.
- Brahim, S.; Narinesingh, D. & Guiseppi-Elie, A. (2002). Bio-smart hydrogels: co-joined molecular recognition and signal transduction in biosensor fabrication and drug delivery. *Biosensors & Bioelectronics*. Vol. 17, No. 11-12, (December 2002), pp. 973-981. ISSN: 09565663.
- Bushetti, S; Singh, V., Raju, S., Atharjaved & Veermaram (2009). Stimuli sensitive hydrogels: A review. *Indian Journal of Pharmaceutical Education and Research*. Vol. 43, No. 3, (July-September 2009), pp.241-250, ISSN: 0019-5464
- de Groot, J; Spaans, C., van Calck, R., van Beijma, F., Norrby, S. & Pennings, A. (2003). Hydrogels for an accommodating intraocular lens. An explorative study. *Biomacromolecules*. Vol. 4 No. 3, (May-June 2003), pp. 608-616, ISSN: 1525-7797.
- Dergunov, S. & Mun, G. (2009). Gamma-irradiated chitosan-polyvinyl pyrrolidone hydrogels as pH-sensitive protein delivery system. *Radiation Physics and Chemistry*. Vol. 78, No. 1, (January 2009), pp. 65-68. ISSN: 0969-806X.
- Devine, D. & Higginbotham, C. (2003). The synthesis of a physically crosslinked NVP based hydrogel. *Polymer*. Vol. 44, No. 26, (December 2003), pp. 7851-7860, ISSN: 0032-3861
- Drury, J., & Mooney, D. (2003). Hydrogels for tissue engineering: scaffold design variables and applications. *Biomaterials*. Vol. 24, No. 24, pp.4337-4351, (November 2003), ISSN 0142-9612.
- Dumitriu, S. (Ed.). (2002). *Polymeric Biomaterials*, Marcel Dekker, Inc., SBN: 0824705696, New York.
- Eichenbaum, G.; Kiser, P., Simon, S. & Needham, D. (1998). pH and ion-triggered volume response of anionic hydrogel microspheres. *Macromolecules*. Vol. 31, No. 15 (July 1998), pp. 5084-5093, ISSN 0024-9297
- Ende, M. & Peppas, N. (1996). Transport of ionizable drugs and proteins in crosslinked poly(acrylic acid) and poly(acrylic acid-co-2-hydroxyethyl methacrylate) hydrogels .1. Polymer characterization. *Journal of Applied Polymer Science*. Vol. 59 No. 4, (January 1996), pp.673-685, ISSN: 0021-8995.
- Flory, P. (1953). *Principles of polymer chemistry*, Cornell University Press. ISBN 0-8014-0134-8 Ithaca, NY.
- Gil, E. & Hudson, S. (2004). Stimuli-responsive polymers and their bioconjugates. *Progress in Polymer Science*. Vol. 29 No. 12, (December 2004), pp. 1173-1222, ISSN: 0079-6700.
- Gupta, P.; Vermani, K. & Garg, S. (2002). Hydrogels: from controlled release to pH-responsive drug delivery. *Drug Discovery Today*. Vol. 7, No. 10, (15 May 2002), pp. 569-579, ISSN: 1359-6446.
- He, C.; Kim, S. & Lee, D. (2008). In situ gelling stimuli-sensitive block copolymer hydrogels for drug delivery. *Journal of Controlled Release*. Vol. 127, No. 3, (May 2008), pp.189-207. ISSN: 0168-3659
- Hennink, W. & van Nostrum, C. (2002). Novel crosslinking methods to design hydrogels. *Advanced Drug Delivery Reviews*. Vol. 54, No. 1 (January 2002), pp.13-36, ISSN 0169-409X
- Hin, T. (2004). *Engineering Materials for Biomedical Applications*. World Scientific Publishing, Singapore, ISBN: 981-256-061-0.

- Hirokawa, Y. & Tanaka, T. (1984). Volume Phase-Transition in a Nonionic Gel. *Journal of Chemical Physics*. Vol. 81, No. 12, pp.6379-6380. ISSN: 0021-9606
- Hoffman, A. S. (2002). Hydrogels for biomedical applications. *Advanced Drug Delivery Reviews*. Vol. 54, No. 1, (January 2002), pp.3-12, ISSN 0169-409X.
- Jabbari, E. & Nozari, S. (1999). Synthesis of Acrylic Acid Hydrogel by  $\gamma$ -Irradiation Cross-linking of Polyacrylic Acid in Aqueous Solution. *Iranian Polymer Journal*. Vol. 8, No. 4, pp. 264-270,ISSN 1735-5265.
- Jeong, B., Y. H. Bae, et al. (1997). Biodegradable block copolymers as injectable drug-delivery systems. *Nature*. Vol. 388, No. 6645, (August 1997), pp.860-862, ISSN: 0028-0836
- Jhon, M. & Andrade, J. (1973). Water and Hydrogels. *Journal of Biomedical Materials Research* Vol. 7, No. 6, pp. 509-522, ISSN 1097-4636.
- Jianqi, F.& Lixia, G. (2002). PVA/PAA thermo-crosslinking hydrogel fiber: preparation and pH-sensitive properties in electrolyte solution. *European Polymer Journal*. Vol. 38, No. 8, (August 2002), pp.1653-1658, ISSN: 0014-3057
- Kabra, B.; Akhtar, M. & Gehrke, S. (1992). Volume Change Kinetics of Temperature-Sensitive Poly(Vinyl Methyl-Ether) Gel. *Polymer*. Vol. 33, No. 5, pp. 990-995. ISSN: 0032-3861
- Kang, S. & Bae, Y. (2003). A sulfonamide based glucose-responsive hydrogel with covalently immobilized glucose oxidase and catalase. *Journal of Controlled Release*. Vol. 86, No. 1, (January 2003), pp.115-121. ISSN: 0168-3659
- Kashyap, N.; Kumar, N, & Ravi Kumar, M. (2005). Hydrogels for pharmaceutical and biomedical applications. *Critical Reviews in Therapeutic Drug Carrier Systems*. Vol. 22, No. 2, pp. 107-149. ISSN: 0743-4863
- Kashyap, N., Kumar, N. & Ravi Kumar (2004). Smart gels for drug delivery applications. *Drug Development and Delivery*. Vol. 4, No. 7 (Sept 2004), pp. 32-39.
- Kim, J.; Lee, S., Kim, S. & Lee, Y. (2002). Rapid temperature/pH response of porous alginate-g-poly(N-isopropylacrylamide) hydrogels. *Polymer*. Vol. 43, No. 26, (December 2002), pp. 7549-7558. ISSN: 0032-3861
- Kim, S.; Kim, H.; Park, S.; Ki, I.; Lee, S.; Lee, T. & Kim, S. (2005). Behavior in electric fields of smart hydrogels with potential application as bio-inspired actuators. *Smart Materials & Structures*. Vol. 14, No. 4, pp.511-514, ISSN 1361-665X
- Kim, S.; Park, S. & Kim, S. (2004). Properties of smart hydrogels composed of polyacrylic acid/poly(vinyl sulfonic acid) responsive to external stimuli. *Smart Materials & Structures*. Vol. 13, No. 2, pp.317-322, ISSN 1361-665X.
- King, A., B. Strand, et al. (2003). Improvement of the biocompatibility of alginate/poly-L-lysine/alginate microcapsules by the use of epimerized alginate as a coating. *J Biomed Mater Res A*. Vol. 64, No. 3, (March 2003),pp.533-539.ISSN 1549-3296.
- Kopecek, J. (2003). Smart and genetically engineered biomaterials and drug delivery systems. *European Journal of Pharmaceutical Sciences*. Vol. 20, No. 1, pp.1-16, ISSN: 1530-9932.
- Kozlovskaya, V.; Kharlampieva, E., Mansfield, M. & Sukhishvili, S. (2006). Poly(methacrylic acid) hydrogel films and capsules: Response to pH and ionic strength, and encapsulation of macromolecules. *Chemistry of Materials*. Vol. 18, No. 2, pp.328-336, ISSN 0897-4756.

- Kubo, M.; Matsuura, T.; Morimoto, H.; Uno, T. & Itoh, T. (2005). Preparation and polymerization of a water-soluble, nonbonding crosslinking agent for a mechanically crosslinked hydrogel. *Journal of Polymer Science Part A-Polymer Chemistry*. Vol. 43, No. 21, pp.5032-5040, ISSN 0887-624X.
- Kunugi, S.; Takano, K, Tanaka, N.; Suwa, K. & Akashi, M. (1997). Effects of pressure on the behavior of the thermoresponsive polymer poly(N-vinylisobutyramide) (PNVIBA). *Macromolecules*. Vol. 30, No. 15, pp.4499-4501, ISSN 0024-9297.
- Lamba, N.; Woodhouse, K. & Cooper, S. (1998). *Polyurethanes in Biomedical Applications.*, CRC Press, ISBN 0849345170, New York.
- Lee, B.; West, B., McLemore, R., Pauken, C. & Vernon, B. (2006). In-situ injectable physically and chemically gelling NIPAAm-based copolymer system for embolization. *Biomacromolecules*. Vol. 7, No. 6, pp.2059-2064. ISSN 1525-7797.
- Lee, K. & Mooney, D. (2001). Hydrogels for tissue engineering. *Chemical Reviews*. Vol. 101, No. 7, pp. 1869-1879, ISSN:0009-2665
- Li, S.; Molina, I.; Martinez, M. & Vert, M. (2002). Hydrolytic and enzymatic degradations of physically crosslinked hydrogels prepared from PLA/PEO/PLA triblock copolymers. *Journal of Materials Science-Materials in Medicine*. Vol. 13, No. 1, pp. 81-86, ISSN: 0957-4530.
- Liu, Y.; Vrana, N. & McGuinness, G. (2009). Physically Crosslinked Composite Hydrogels of PVA With Natural Macromolecules: Structure, Mechanical Properties, and Endothelial Cell Compatibility. *Journal of Biomedical Materials Research Part B-Applied Biomaterials*. Vol. 90B, No. 2, pp. 492-502, ISSN: 1552-4981
- Xuequan, L.; Maolin, Z.; Jiuqiang, L. & Hongfei, H. (2000). Radiation preparation and thermo-response swelling of interpenetrating polymer network hydrogel composed of PNIPAAm and PMMA. *Radiation Physics and Chemistry*. Vol. 57, No. 3-6, (March 2000), pp.477-480, ISSN: 0969-806X.
- Lu, Z.; Kopeckova, P. & Kopecek, J. (2003). Antigen responsive hydrogels based on polymerizable antibody Fab ' fragment. *Macromolecular Bioscience*. Vol. 3, No. 6, pp. 296-300, ISSN 1616-5195
- Mequanint, K.; Patel, A.; Bezuidenhout, D. (2006). Synthesis, swelling behavior, and biocompatibility of novel physically cross-linked polyurethane-block-poly(glycerol methacrylate) hydrogels. *Biomacromolecules*. Vol. 7, No. 3, pp. 883-891. ISSN 1525-7797.
- Merrett, K.; Liu, W.; Mitra, D.; Camm, K.; McLaughlin, C.; Liu, Y.; Watsky, M.; Li, F.; Griffith, M. & Fogg, D. (2009). Synthetic neoglycopolymer-recombinant human collagen hybrids as biomimetic crosslinking agents in corneal tissue engineering. *Biomaterials*. Vol. 30, No. 29, pp.5403-5408, ISSN: 0142-9612
- Millon, L. & Wan, W. (2006). The polyvinyl alcohol-bacterial cellulose system as a new nanocomposite for biomedical applications. *Journal of Biomedical Materials Research Part B-Applied Biomaterials*. Vol. 79B, No. 2, pp.245-253. ISSN: 1552-4981
- Miura, S.; Teramura, Y. & Iwata, H. (2006). Encapsulation of islets with ultra-thin polyion complex membrane through poly(ethylene glycol)-phospholipids anchored to cell membrane. *Biomaterials*. Vol. 27, No. 34, (December 2006), pp. 5828-5835. ISSN: 0142-9612
- Miyata, T.; Asami, N. & Urugami, T. (1999). A reversibly antigen-responsive hydrogel. *Nature*. Vol. 399, No. 6738, pp.766-769. ISSN: 0028-0836

- Miyata, T., Uragami, Nakamae, K (2002). Biomolecule-sensitive hydrogels. *Advanced Drug Delivery Reviews*. Vol. 54, No. 1, (January 2002), pp.79-98, ISSN 0169-409X.
- Nicolson, P. & Vogt, J. (2001). Soft contact lens polymers: an evolution. *Biomaterials*. Vol. 22, No. 24, pp.3273-3283, ISSN: 0142-9612.
- Obaidat, A. & Park, K. (1996). Characterization of glucose dependent gel-sol phase transition of the polymeric glucose-concanavalin A hydrogel system. *Pharmaceutical Research* Vol. 13, No. 7, pp.989-995. ISSN: 0724-8741
- Orive, G.; Hernández, R.; Gascón, A.; Calafiore, R.; Chang, T.; De Vos, P.; Hortelano, G.; Hunkeler, D.; Lacík, I.; Shapiro, J. & Pedraz, J. (2003). Cell encapsulation: promise and progress. *Nature Medicine*. Vol. 9, No. 1, pp.104-107, ISSN: 1078-8956.
- Orive, G.; Hernández, R.; Gascón, A.; Calafiore, R.; Chang, T.; De Vos, P.; Hortelano, G.; Hunkeler, D.; Lacík, I. & Pedraz, J. (2004). History, challenges and perspectives of cell microencapsulation. *Trends in Biotechnology*. Vol. 22, No. 2, (February 2004), pp. 87-92, ISSN: 0167-9430
- Park, J. & Bae, Y. (2002). Hydrogels based on poly(ethylene oxide) and poly(tetramethylene oxide) or poly(dimethyl siloxane): synthesis, characterization, in vitro protein adsorption and platelet adhesion. *Biomaterials*. Vol. 23, No. 8: 1797-1808. ISSN: 0142-9612
- Patel, A.; Fine, B., Sandig, M. & Mequanint, K. (2006). Elastin biosynthesis: The missing link in tissue-engineered blood vessels. *Cardiovascular Research*. Vol. 71. No. 1, pp. 40-49, ISSN 2151-920X.
- Peppas, N.; Bures, P.; Leobandung, W. & Ichikawa, H. (2000). Hydrogels in pharmaceutical formulations. *European Journal of Pharmaceutics and Biopharmaceutics*. Vol. 50, No. 1, pp. 27-46, ISSN 0939-6411.
- Peppas, N.; Hilt, J.; Khademhosseini, A. & Langer, R. (2006). Hydrogels in biology and medicine: From molecular principles to bionanotechnology. *Advanced Materials*. Vol. 18, No, 11, (May 2006), pp. 1345-1360, ISSN: 1521-4095
- Peppas, N.; Huang, Y.; Torres-Lugo, M.; Ward, J. & Zhang J. (2000). Physicochemical, foundations and structural design of hydrogels in medicine and biology. *Annual Review of Biomedical Engineering*. Vol. 2, (August 2000), pp.9-29, ISSN:1523-9829.
- Podual, K.; Doyle, F. & Peppas, N. (2000). Glucose-sensitivity of glucose oxidase-containing cationic copolymer hydrogels having poly(ethylene glycol) grafts. *Journal of Controlled Release*. Vol. 67, No. 1, (June 2000), pp. 9-17, ISSN: 0168-3659
- Podual, K.; Doyle, F. & Peppas, N. (2000). Preparation and dynamic response of cationic copolymer hydrogels containing glucose oxidase. *Polymer*. Vol. 41, No. 11, (May 2000), pp. 3975-3983, ISSN: 0032-3861.
- Xiangli, Q.; Zhenjia, Z. & Side, Y. (2006). Preparation of initiator and cross-linker-free poly (N-isopropylacrylamide) nanogels by photopolymerization. *Journal of Photochemistry and Photobiology A-Chemistry*. Vol. 177, No. 2-3, (January 2006), pp. 191-196, ISSN: 1010-6030.
- Qu, X.; Wirsen, A. & Albertsson (2000). Novel pH-sensitive chitosan hydrogels: swelling behavior and states of water. *Polymer*. Vol. 41, No. 12, (June 2000), 4589-4598. ISSN: 0032-3861.
- Ratner, B.; Hoffman, A.; Schoen, F. & Lemons, J. (2004). *Biomaterials Science: An Introduction to Materials in Medicine*, Elsevier Academic Press, ISBN 0-12-582463-7, San Diego, CA.

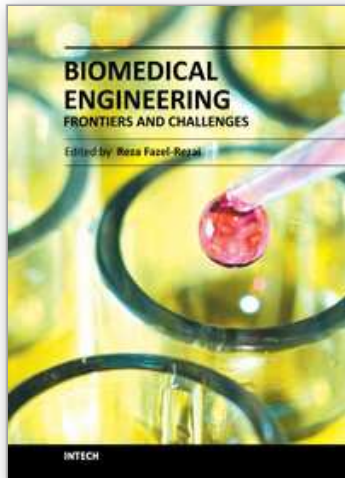
- Ritger, P. & Peppas, N. (1987). A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *Journal of Controlled Release*. Vol. 5, No. 1, (June 1987), pp. 23-36, ISSN: 0168-3659
- Rogero, S.; Malmonge, S.; Lugao, A.; Ikeda, T.; Miyamaru, L. & Cruz, A. (2003). Biocompatibility study of polymeric biomaterials. *Artificial Organs*. Vol. 27, No. 5, (May 2003), pp. 424-427, ISSN: 1525-1594.
- Rosiak, J. & Yoshii, F. (1999). Hydrogels and their medical applications. *Nuclear Instruments & Methods in Physics Research Section B-Beam Interactions with Materials and Atoms*. Vol. 151, No. 1-4, pp.56-64, ISSN: 0168-583X
- Ruel-Gariepy, E. & Leroux, J. (2004). In situ-forming hydrogels - review of temperature-sensitive systems. *European Journal of Pharmaceutics and Biopharmaceutics*. Vol. 58, No. 2, pp. 409-426. ISSN: 0939-6411
- Schmaljohann, D. (2005). Thermo-responsive polymers and hydrogels in tissue engineering. *e-Polymers*. No. 021, pp. 1-17, ISSN 1618-7229
- Schmaljohann, D.; Oswald, J.; Jørgensen, B.; Nitschke, M.; Beyerlein, D. & Werner, C. (2003). Thermo-responsive PNiAAm-g-PEG films for controlled cell detachment. *Biomacromolecules*. Vol. 4, No. 6, (August 2003), pp.1733-1739. ISSN 1525-7797
- Sen, M. & Avci, E. (2005). Radiation synthesis of poly(N-vinyl-2-pyrrolidone)-kappa-carrageenan hydrogels and their use in wound dressing applications. I. Preliminary laboratory tests. *Journal of Biomedical Materials Research Part A*. Vol. 74A, No. 2, pp.187-196 ISSN: 1549-3296.
- Sen, M. & Sari M. (2005). Radiation synthesis and characterization of poly(N,N-dimethylaminoethyl methacrylate-co-N-vinyl 2-pyrrolidone) hydrogels. *European Polymer Journal*. Vol. 41, No. 6, pp.1304-1314. ISSN 0014-3057
- Shiino, D.; Murata, Y.; Kubo, A.; Kim, Y.; Kataoka, K.;Koyama, Y.; Kikuchi, A.; Yokoyama, M.; Sakurai, Y. & Okano, T. (1995). Amine containing phenylboronic acid gel for glucose-responsive insulin release under physiological pH. *Journal of Controlled Release*. Vol. 37, No. 3, pp. 269-276, ISSN: 0168-3659
- Silva, A.; Richard, C.; Bessodes, M.; Scherman, D. & Merten, O. (2009). Growth factor delivery approaches in hydrogels. *Biomacromolecules*. Vol. 10, No.1 (November 26, 2008) pp.9-18. ISSN 1525-7797
- Slaughter, B.; Khurshid, S. Fisher, O.; Khademhosseini, A. & Peppas, N. (2009). Hydrogels in regenerative medicine. *Advanced Materials*. Vol. 21, pp. 3307-3329. ISSN: 1521-4095
- Song, M.; Lee, D.; Ahn, J.; Kim, D. & Kim, S. (2000). Dielectric behavior during sol-gel transition of PEO-PPO-PEO triblock copolymer aqueous solution. *Polymer Bulletin* Vol. 43, No. 6, pp. 497-504, ISSN 1436-2449.
- Stabenfeldt, S.; Gacia, A. & LaPlaca, M. (2006). Thermoreversible laminin-functionalized hydrogel for neural tissue engineering. *Journal of Biomedical Materials Research Part A*. Vol. 77A, No. 4, pp. 718-725. ISSN 1549-3296.
- Stile, R. & Healy, K. (2001). Thermo-responsive peptide-modified hydrogels for tissue regeneration. *Biomacromolecules*. Vol. 2, No. 1, pp.185-194. ISSN 1525-7797
- Suwa, K.; Morishita, K.; Kishida, A. & Akashi, M. (1997). Synthesis and functionalities of Poly(N-vinylalkylamide) .5. Control of a lower critical solution temperature of poly(N-vinylalkylamide). *Journal of Polymer Science Part A-Polymer Chemistry*. Vol. 35, No. 15, pp. 3087-3094. ISSN: 1099-0518

- Suwa, K.; Wada, Y. & Akashi, M. (1997). Synthesis and functionalities of poly(N-vinylalkylamide) .6. A novel thermosensitive hydrogel crosslinked poly(N-vinylisobutyramide). *Journal of Polymer Science Part A-Polymer Chemistry*. Vol.35, No. 16, pp.3377-3384, ISSN: 0887-624X.
- Theiss, D.; Schmidt, T. & Arndt K-F. (2004). Temperature-sensitive poly(vinyl methyl ether) hydrogel beads. *Macromolecular Symposia*. Vol. 210, No. 1, (March 2004), pp.465-474, ISSN:1521-3900
- Traitel, T.; Cohen, Y. & Kost, J. (2000). Characterization of glucose-sensitive insulin release systems in simulated in vivo conditions. *Biomaterials*. Vol. 21, No. 16, pp. 1679-1687. ISSN: 0142-9612
- Vamvakaki, M.; Palioura, D.; Spyros, A.; Armes, S. & Anastasiadis, S. (2006). Dynamic light scattering vs H-1 NMR investigation of pH-responsive diblock copolymers in water. *Macromolecules*. Vol. 39, No. 15, (July 2006), pp.5106-5112. ISSN 1525-7797
- Vinatier, C.; Magne, D.; Weiss, P.; Trojani, C.; Rochet, N.; Carle, G.; Vignes-Colombeix, C.; Chadjichristos, C.; Galera, P.; Daculsi, G. & Guicheux, J. (2005). A silanized hydroxypropyl methylcellulose hydrogel for the three-dimensional culture of chondrocytes. *Biomaterials*. Vol. 26, No. 33, (November 2005) pp 6643-6651. ISSN: 0142-9612
- Wang, C.; Stewart, R. & Kopecek, J. (1999). Hybrid hydrogels assembled from synthetic polymers and coiled-coil protein domains. *Nature* Vol. 397, No. 6718, (February 1999), pp. 417-420, ISSN : 0028-0836
- Wang, Y.; Shen, Y.; Zhang, Y.; Yue, B. & Wu, C. (2006). pH-sensitive polyacrylic acid (PAA) hydrogels trapped with polysodium-p-styrenesulfonate (PSS). *Journal of Macromolecular Science Part B-Physics*. Vol. 45, No. 4, pp.563-571. ISSN 1525-609X
- Wichterle, O. & Lim, D. (1960). Hydrophilic Gels for Biological Use. *Nature*. Vol. 185, No. 4706, pp.117-118, ISSN : 0028-0836.
- Wright, E. & Conticello, V. (2002). Self-assembly of block copolymers derived from elastin-mimetic polypeptide sequences. *Advanced Drug Delivery Reviews*. Vol. 54, No. 8, pp. 1057-1073, ISSN 0169-409X.
- Wright, E. R., R. A. McMillan, et al. (2002). Thermoplastic elastomer hydrogels via self-assembly of an elastin-mimetic triblock polypeptide. *Advanced Functional Materials* Vol. 12, No. 2, pp.149-154, ISSN: 1616-3028.
- Xu, C.; Breedveld, V. & Kopeček, J. (2005). Reversible hydrogels from self-assembling genetically engineered protein block copolymers. *Biomacromolecules*. Vol. 6, No. 3, (April 2005), pp.1739-1749, ISSN 1525-7797.
- Yaszemski, M.; Trntolo, D.; Lewandrowski, K-U.; Hasirci, V.; Altobelli, D. & Wise, D. (Eds.), (2004). *Tissue Engineering and Novel Delivery Systems*, CRC Press, ISBN-13: 978-0824747862
- Ying, Y.; Gu, X. & Yang, C. (1998). Abnormal pH sensitivity of polyacrylate-polyurethane hydrogels. *Journal of Applied Polymer Science*. Vol. 70, No. 6, (November 1998), pp. 1047-1052. ISSN: 0021-8995.
- Yui, N.; Mrsny, R. & Park, K. (Eds.), (2004). *Reflexive Polymers and Hydrogels: Understanding and Designing Fast Responsive Polymeric Systems*, CRC Press, ISBN: 978-0-8493-1487-2, New York.

Zan, J.; Chen, H.; Jiang, G.; Lin, Y. & Ding F. (2006). Preparation and properties of crosslinked chitosan thermosensitive hydrogel for injectable drug delivery systems. *Journal of Applied Polymer Science*. Vol. 101, No. 3, pp.1892-1898. ISSN: 0021-8995.

IntechOpen

IntechOpen



## **Biomedical Engineering - Frontiers and Challenges**

Edited by Prof. Reza Fazel

ISBN 978-953-307-309-5

Hard cover, 374 pages

**Publisher** InTech

**Published online** 01, August, 2011

**Published in print edition** August, 2011

In all different areas in biomedical engineering, the ultimate objectives in research and education are to improve the quality life, reduce the impact of disease on the everyday life of individuals, and provide an appropriate infrastructure to promote and enhance the interaction of biomedical engineering researchers. This book is prepared in two volumes to introduce recent advances in different areas of biomedical engineering such as biomaterials, cellular engineering, biomedical devices, nanotechnology, and biomechanics. It is hoped that both of the volumes will bring more awareness about the biomedical engineering field and help in completing or establishing new research areas in biomedical engineering.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Alpesh Patel and Kibret Mequanint (2011). Hydrogel Biomaterials, Biomedical Engineering - Frontiers and Challenges, Prof. Reza Fazel (Ed.), ISBN: 978-953-307-309-5, InTech, Available from:

<http://www.intechopen.com/books/biomedical-engineering-frontiers-and-challenges/hydrogel-biomaterials>

# **INTECH**

open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821



© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](#), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen