2

Hydrogels and its Nanocomposites from Renewable Resources: Biotechnological and Biomedical Applications

B. Manjula[1]*, A. Babul Reddy[1], T. Jayaramudu[1], E. R. Sadiku[1], Oluranti Agboola[2] and Tauhami Mokrani[2]

[1]*Department of Chemical, Metallurgical and Materials Engineering, Tshwane University of Technology, Pretoria, Republic of South Africa*
[2]*Department of Civil and Chemical Engineering, University of South Africa, Johannesburg, Republic of South Africa*

Abstract

Eco-friendly hydrogel and its nanocomposite (NC) hydrogels prepared from renewable resources have drawn significant attention from industrial and academic sectors. The eco-friendly polymeric hydrogels contain polymers or their composites, which are either biodegradable or biobased (from renewable resources). Their carbon-neutral lifecycle may reduce the emission of carbon dioxide and the dependence on petroleum-based materials and then reduce the human footprint on the environment. In this concern, the technologies are required in order to develop novel soft materials beside to get the new information, and fundamental understanding results in important advancement in the field of hydrogels and its NC hydrogels. A wide diversity of complex hydrogel structures have been found with distinct physical, chemical, and biological properties at the nanometer level. The possibility in order to develop self-assembled and supramolecular morphologies makes natural polymers and inorganic nanoparticles desirable building blocks for the design of water-based gels. In this book chapter, we partially covered the accomplishments and trends in the field of NC polymer hydrogels with a focus on creative approaches to generating structures, properties, and function within mostly biotechnological and biomedical applications.

Keywords:

2.1 Introduction

In recent years, hydrogels made up from renewable resources have received great attention due to their unique properties results used in various applications (Lee, 1991; Li *et al*., 2013). Hydrogels hold their own degree of flexibility due to their high water

**Corresponding author*: manjubandla@gmail.com

Vijay Kumar Thakur, Manju Kumari Thakur and Michael R. Kessler (eds.), Handbook of Composites from Renewable Materials, Volume 7, (67–96) © 2017 Scrivener Publishing LLC

content, which is very similar to natural tissue (Thakur & Thakur, 2014a,b). Most of the researchers defined the term 'hydrogels' in many dissimilar ways, but the majority of them saying that hydrogel is a water-swollen and cross-linked polymeric network provided by the facile reaction between one or more monomers. Another definition also familiar to hydrogels is a polymeric material that displays the potentially to swell and hold a significant amount of water within its hydrogel structure, but will not dissolve in water. The large amount of water swollen efficiency of hydrogels appear from hydrophilic (water loving) functional groups attached to the polymeric backbone, while their resistance to dissolution appear from cross-links between network chains (Thakur & Thakur, 2015). As consequence of water-swollen and cross-kinked polymeric hydrogel is also considered as an open vessel through semipermeable boundaries, across which solute and water molecules can move, whereas charged (ionizable) groups fixed on the network chains cannot move (Figure 2.1).

In the last two decades, natural hydrogels were slowly replaced by synthetic hydrogels which has long service life, high capacity of water absorption and high gel strength. Polysaccharides (starch, chitosan, alginate, etc.) are widely used to develop a novel natural hydrogels (biohydrogels) that have advantages of low toxicity, biodegradability, biocompatibility, and availability from renewable resources (Coviello *et al*., 2007). Indeed, polysaccharides are the most abundant and readily obtained from renewable sources, such as cultures of microbial selected strains, the algal and plant kingdoms as well as through recombinant DNA techniques. Therefore, the polysaccharides have a wide diversity of composition and properties that cannot be easily mimicked in a general chemical laboratories and the ease of their fabrication makes several polysaccharides are cheaper than synthetic polymers (Coviello *et al*., 2007). Fortunately, synthetic polymers generally ensure well-defined structures that can be altered to yield functionality and degradability as well as they are more stable even in harsh conditions and strong fluctuations of temperatures (Ahmed, 2015). The most important objective of hydrogel based technology is the development of injectable hydrogels (IHs). The schematic representation of IHs was shown in Figure 2.2. From this figure, an aqueous mixture of bioactive agents and hydrogel precursors are administered once inside the body using a syringe and gelates. The hydrogel precursors can gelate under mild conditions only due to physical changes, such as temperature, pH value, ionic concentration,

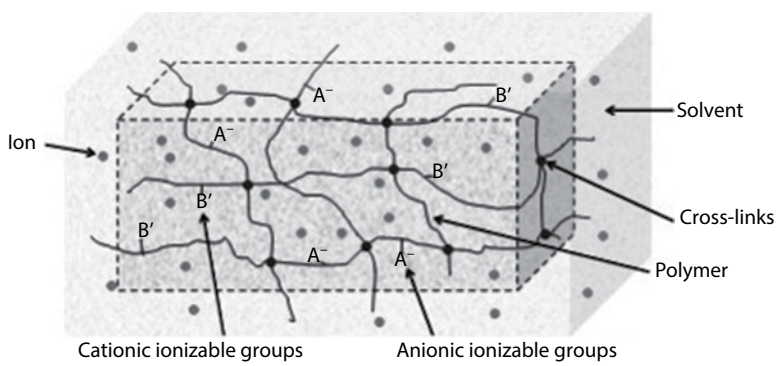

Figure 2.1 A simplified representation of a hydrogel immersed in a solvent.

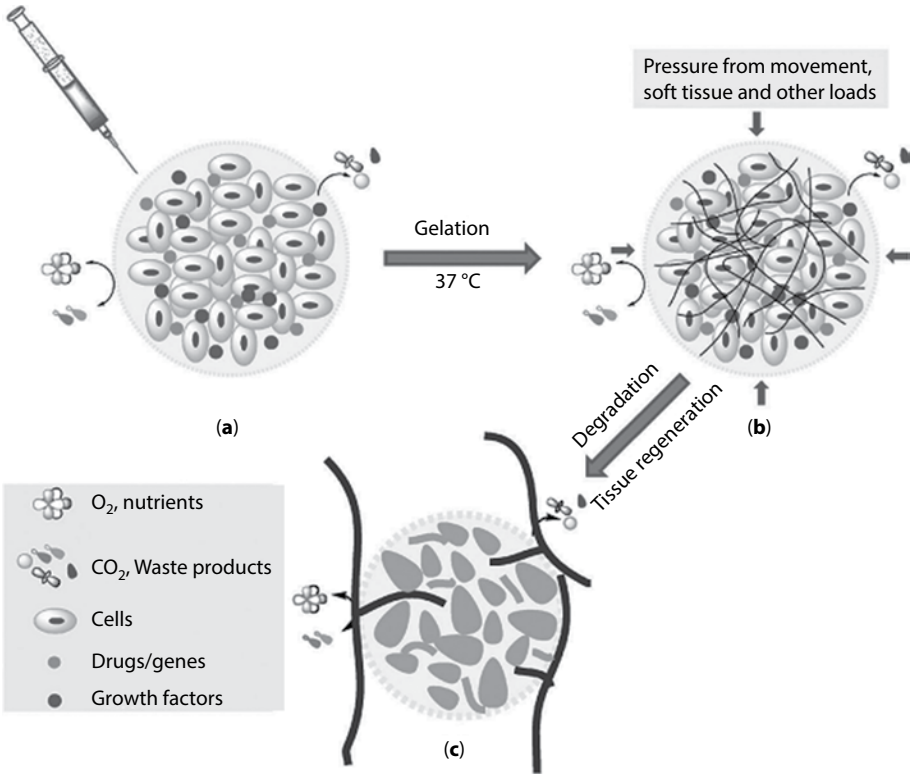

Figure 2.2 Schematic explanation of IHs for biomedical applications (Li *et al*., 2012).

and/or chemical reactions, like Schiff base, Michael addition, disulfide bond formation, etc. (Nguyen & Lee, 2010). The advantages of using IHs depend on their high moldability, chance of *in vivo* delivery in a marginally offensive way and ability of easy and effective encapsulation of cells and/or drugs. After existence delivered *in vivo*, IHs form tissue constructs *in situ*, providing local mechanical and biological cues that may expand tissue regeneration (Bryers *et al*., 2012; Wang *et al*., 2010). Thus, IHs possesses numerous applications in the pharmaceutical and biomedical fields, such as vehicles for drug/gene/cell delivery and tissue engineering.

Furthermore, hydrogels can be made that show unique character of natural living tissue and stimuli-responsive swelling behavior. In general, the hydrogels are water-swollen networks at which polymer chains are connected to each other with physical or chemical intersections (Peppas *et al*., 1985). Hydrogels are classified in different categories (see Figure 2.7) based on their network structure. For instance, depending on the fashion that cross-links are formed, they are divided into two classes, such as chemical hydrogels (involve of covalently cross-linked network) and physical hydrogels (are formed by secondary interactions, such as ionic bonds, hydrogen bonds, hydrophobic interactions, and crystallites) and entangled hydrogels. Chemical hydrogels are commonly prepared in two different ways: 'three-dimensional polymerization' (Figure 2.3a), in which a hydrophilic monomer is polymerized in the presence of a polyfunctional cross-linking agent, or by direct cross-linking of water-soluble polymers

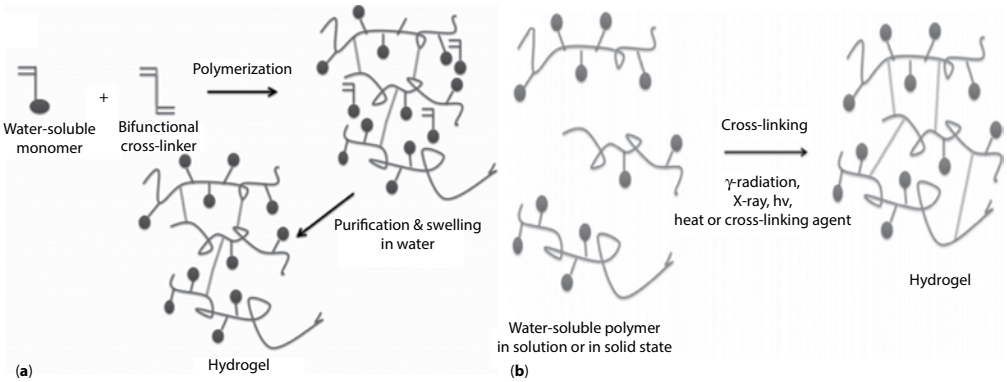

Figure 2.3 (a) Synthesis of hydrogels by three-dimensional polymerization and (b) synthesis of hydrogels by cross-linking of ready-made water-soluble polymers (Caló & Khutoryanskiy, 2015).

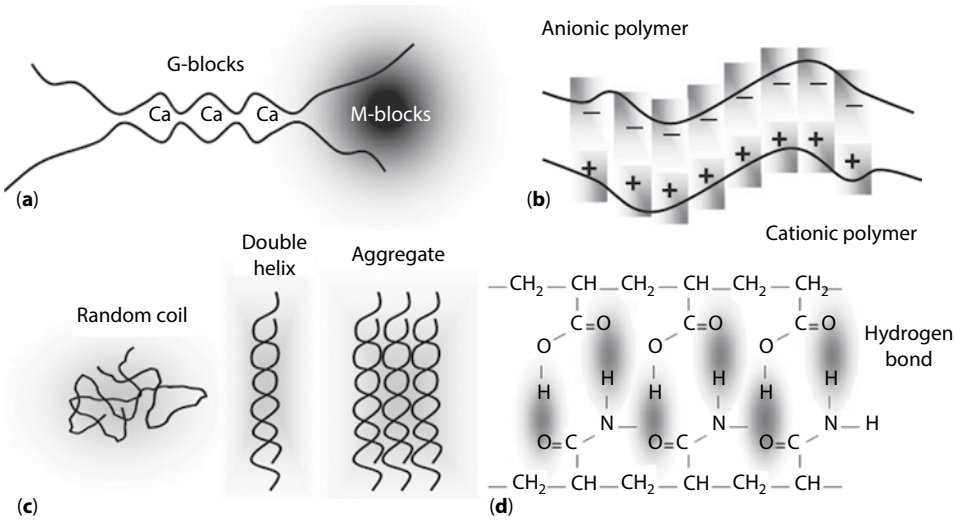

Figure 2.4 Schematic illustration of different physical hydrogels cross-linked by (a) ion–polymer complexation, (b) polymer–polymer complexation, (c) chain aggregation, and (d) hydrogen bonding (Omidian & Park, 2012).

(Figure 2.3b). Polymerization is usually initiated by free-radical generating compounds such as benzoyl peroxide, 2,2-azo-isobutyronitrile (AIBN), and ammonium peroxodisulfate or by using UV, gamma or electron beam radiation. However, three-dimensional polymerization often results in materials containing significant levels of residual monomers and therefore purification of these materials has to be performed thoroughly because the unreacted monomers are often toxic and could leach out from the hydrogels continuously. The purification of hydrogels containing residual monomers is typically performed by extraction into excess water, and can take up to several weeks to be completed (Mathur *et al.*, 1996; Montoro *et al.*, 2014).

In physical hydrogels, the nature of the cross-linking process is physical. This is generally attained *via* using physical processes, such as aggregation, complexation, association, crystallization, and hydrogen bonding. Figure 2.4a–d shows different kind of

approaches in order to make a chemical and physical hydrogels, respectively. While chemical hydrogels are permanent and irreversible as a result of configurationally changes, physical hydrogels are reversible due to the conformational changes. In contrast, entanglement hydrogels are formed through physical interactions of polymer chains twisting and wrapping around each other. These are formed either in the melt or in solution phase results the relative molecular weight of polymer involved in hydrogel systems is becomes bigger than the critical entanglement molecular weight of the polymer. Entanglement network system will dissolve with the adding of an excess amount of solvent to form more dilute solutions. Therefore, the current research on entangled network systems is focused on forming so-called interpenetrating networks (IPNs) such as semi-IPNs or double-network hydrogels (Calvert, 2009; Gong *et al*., 2003; Han *et al*., 2008; Myung *et al*., 2008). These systems contain two or more kind of polymers and the first polymer network is chemically cross-linked, but the second one is non-cross-linked and highly entangled and filling the voids of the first network. The formation of physical entanglements act as soft continuous phase and improve the energy dissolution of the whole network system, resulting in improved mechanical strength and toughness. This type of hydrogel system can be widely used for biomedical applications particularly articular cartilage replacement (Yasuda *et al*., 2005). Hydrogels including two or more components are designed not only to improve swelling ability, biocompatibility, stimuli responsiveness, and morphology, but also to enhance mechanical properties (Čulin *et al*., 2005; Li *et al*., 2009).

2.2 Hydrogels from Renewable Resources

In recent years, materials fabricated from renewable resources have acquire increased their importance as fossil fuels become less available. Particularly, forest by-products from bark, low-value trees, and residue from sawmills offer an alternative as renewable resources. Materials obtained from forest biomass are finding in various applications where biodegradability and biocompatibility are playing significant role. However, the extraction and bifurcation of forest biomass can handle carefully and the outcome of the chemicals converted into high-value products. For example, hemicellulose obtained from cellulose and lignin and this is a heteropolysaccharides existing in annual plants and the cell wall of wood together with cellulose and lignin (Timell, 1967). In addition, hemicellulose is the second most abundant polysaccharide in nature, representing about 20–35% of lignocellulosic biomass (Timell, 1967) and numerous potential applications of hemicelluloses and their derivatives have been explained in detail in the literature (Ebringerová, 2005). The most important advantages of natural polymers from renewable resources include biodegradability, inherent biocompatibility, low toxicity, low cost, and having biologically active moieties that hold up cellular activities (Barbucci *et al*., 2003; Lin & Metters, 2006). As consequence of these facts recently most of the researchers focus on the utilizing the natural materials in order to fabricated the new hydrogels for various applications. The natural materials such as polysaccharides (alginate, chitosan, dextran, hyaluronic acid, etc.) and proteins (collagen, fibrin, gelatin, etc.) are the two major classes of natural biopolymers have been used to fabricate the hydrogels for pharmaceutical and biomedical applications (Kadokawa *et al*., 2007).

For instance, chitosan is an important biopolymer obtained from renewable resources and it is polycationic, antibacterial, bioadhesive, and biocompatible due to its positive charge of $-NH_2$ (lone pair of electrons on nitrogen responsible for cationic behavior) group in acidic medium and can be degraded by human enzymes (lysozyme). Generally, chitosan hydrogels developed through either physical nor chemical ways are becomes to be pH sensitive and are suitable for controlled drug delivery system (Berger *et al.*, 2004). Unfortunately, natural hydrogels developed by natural resources are mechanically weak, to overcome this problem to blending with synthetic polymers in order to improve their mechanical properties (Schoof *et al.*, 2001).

2.3 Hydrogel Technical Features

The functional features of an ideal hydrogel material can be listed as follows (Ahmed, 2015):

- The highest absorption capacity in saline
- pH neutrality after swelling in water
- The lowest price
- The lowest soluble content and residual monomer
- Desired rate of absorption depending on the application requisite
- The highest absorbency under load
- The highest biodegradability without formation of toxic species following the degradation
- The highest durability and stability in the swelling environment during the storage
- Colorlessness, odorlessness, and absolute nontoxic
- Photo stability
- Re-wetting capability of the hydrogel has to be able to give back the absorbed solution or to maintain it; depending on the application.

2.4 Nanocomposite Hydrogels

Recent decades, important innovations have been made as a result of the design of nanocomposite hydrogels (NC gels) and most of the outdated confines of hydrogels have been overcome. NC gels are developed through *in situ* free-radical polymerization under mild conditions (ambient temperature, without stirring) to yield numerous shapes and superficial forms are readily achieved and to produced high toughness and excellent optical properties and stimulus-sensitivity are concurrently understood in NC gels, this may happen unique organic (polymer)/inorganic (clay) network structure, which exhibit a number of fascinating new characteristics. The inorganic component plays a key role in hydrogel network additionally it is available at nanometer scale to open a doors to fabricate the hydrogels at the nano level (Lovinger, 2005). Nano- and biotechnologies provide promising ways in order to develop complex and optimized soft materials with symbiotic properties. Therefore, the possibilities to control physical

and chemical properties through the design of 3D gel structures provide a robust strategy for incorporation of various inorganic components into engineering hydrogels at the nanometer scale.

The outline of this section explains in detail about the structures and properties of NC gels made up primarily from synthetic materials. The majority of publications in the literature mainly focus on exploiting the poly(acryl amide) (PAAm), poly(ethylene oxide) (PEO), or poly(vinyl alcohol) (PVA) polymers in order to develop NC gels. Therefore, NC gels covering these polymers will accept the majority of our courtesy in this chapter. In addition, we will also trying to disclose the polymer–metal, polymer–magnetic and natural polymer NC gels. Since NC polymer hydrogels are sometimes difficult to classify when compared to NC gels, we use here one of the more simplified definitions according to Weiss and Terech, '…if it looks like 'Jell-O', it must be a gel!' (Weiss & Terech, 2006). Many definitions for hydrogels are explained in earlier sections and but researchers never agree always on 'what is a hydrogel'. Therefore, we will try to analyzing the literature based on NC hydrogels and gels obtained from a wide variety of polymers and inorganic nanoparticles at different sizes. According to many scientists the NC polymer hydrogels may be defined as 'cross-linked polymer networks swollen with water in the presence of nanostructures or nano particles'. The polymer is cross-linked to provide a hydrogel network through physical or chemical interactions (see Figure 2.5). The physical interactions are non-covalent in nature and often a result of hydrophobic, ionic interactions and hydrogen bonding, where as in the chemical interactions the cross-linking is stable owing to covalent bonds. The cross-linked polymer networks are able to reversible change in response to external stimuli such as pH, (de)swelling, and temperature. The nanoparticles significantly used to either cross-link the hydrogel in order to adsorb or to add new properties to the hydrogel or attach to polymer chains by simply being entrapped within the hydrogel network. Therefore, nanoparticles support to get unique physical properties of hydrogels such as thermal, sound, barrier, optical, responsible to mechanical, magnetic, electric stimulation, etc. These unique properties directed too many applications in the sensors, actuators, electronics, optics and microfluidics sectors, in addition to separation devices, catalysis, drug delivery and many other biotechnological fields. The combination of natural and synthetic polymers with nanoparticles and biomolecules are very interesting to formulations of various materials. Synergistically allows combining valuable physical, chemical and biological properties to provide NC hydrogels that backing the regeneration and repair of human tissues and body functions.

In order to improve their mechanical properties, different techniques such as the double networks, formation of IPNs, fiber reinforcement, and formation of crystallites have been employed. Recently, novel hydrogels with outstanding mechanical performance and unique network structure have been developed (Haraguchi, 2007; Schexnailder & Schmidt, 2009; Tanaka *et al.*, 2005). Haraguchi *et al.* synthesized NC hydrogels with unique organic-inorganic network structures that showed tremendous optical as well as mechanical performance and swelling/de-swelling properties (see Figure 2.6) (Haraguchi & Takehisa, 2002). In their research, water-swellable silicate nanosheets (3 nm in 25 thicknesses and 30 nm in diameter) were used as vastly multifunctional cross-linking agents. By performing *in situ* polymerization of specific monomers, initiators attached to nanoclay surfaces which were used as

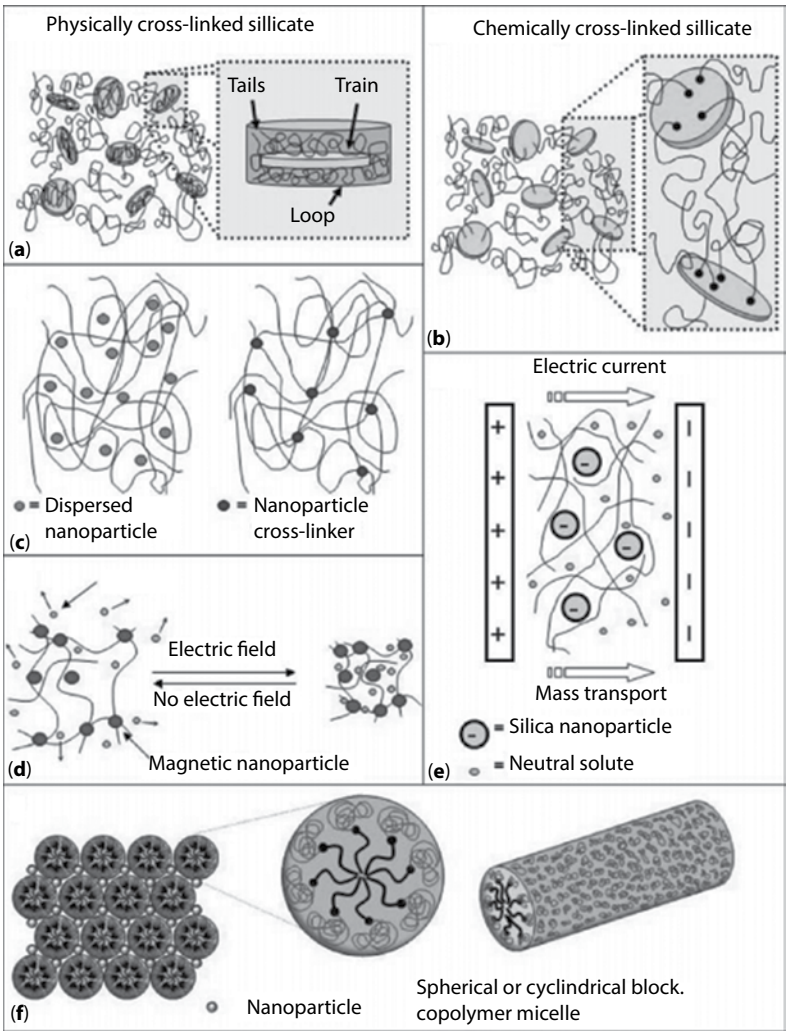

Figure 2.5 Schematic illustration of (a) PEO chains are physically absorb and desorb on the surface of clay particles (Nelson & Cosgrove, 2004a), (b) polymers (PAAm and PNIPAAm) are chemically bonded to the surface of clay (Haraguchi *et al.*, 2005; Zhu *et al.*, 2006), (c) inclusion of Ag and Au metal nanoparticles dispersed within hydrogels network (Murali Mohan *et al.*, 2007; Zhao *et al.*, 2005), (Nelson & Cosgrove, 2004a; Zhu *et al.*, 2006), (d) polymer–magnetic NCs for the release of drugs (Liu *et al.*, 2008; Satarkar & Hilt, 2008), (e) negatively charged silica nanoparticles are immobilized within a PAAm matrix (Matos *et al.*, 2006), and (f) block-copolymer hydrogel model with nanoparticles occupying in the interstitial space between neighboring micelles (Pozzo & Walker, 2007, 2008).

grafting sites for growing polymer chains. Therefore, the formation of extended polymer chains are uniformly distributed between nanoclay particles resulted NC hydrogels were tough, strong, optically transparent, and highly extensible and can absorb high amounts of water compared to traditional hydrogels. Huang *et al.* (2007) have recently developed macromolecular microspheres (MMS) composite hydrogels (MMC gels) with high toughness and strength by means of a identical

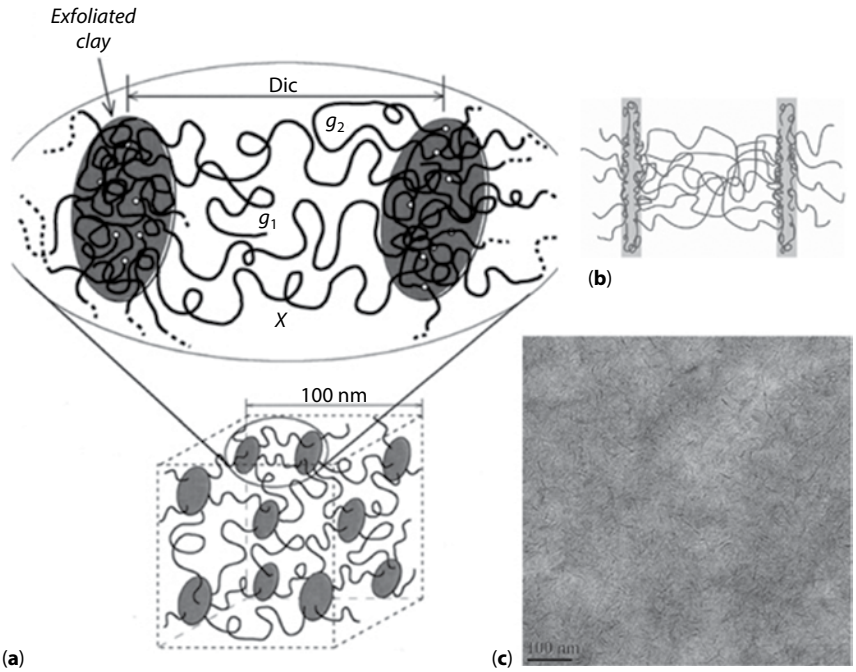

Figure 2.6 (a) Schematic representation of the NC hydrogels structural model with organic/inorganic networks (Haraguchi & Li, 2009; Haraguchi & Takehisa, 2002; Haraguchi *et al*., 2002), (b) illuminate clay platelet model sandwiched by polymer layer (Miyazaki *et al*., 2007), and (c) transmission electron micrographs of NC hydrogel (Flory & Rehner, 1943; Haraguchi *et al*., 2002).

approach to NC hydrogels. In their research, a suspension of MMS brings peroxide groups were irradiated in order to initiate the polymerization of monomers and to produce hydrogels. In this concern, MMS carry out as highly multifunctional cross-linking agents. However, the cross-link density and inter cross-linking distance can be easily alter via changing of monomer, initiator and MMS concentration. MMC hydrogels showed about 120 times stronger than traditional hydrogels and compactable up to about 98% without fracture and they rapidly pick up their original shape.

2.4.1 Polymer-clay-based Nanocomposite Hydrogels

Incorporating the clay nanoparticles into hydrogel network led better mechanical properties. However, the charged clay nanoparticles may exfoliate easily in water due to the colloidal interactions that stabilize the developed hydrogel. Generally, nanoparticles are neither charged nor stabilized via polymer or salt typically aggregate and such aggregates play key role in the mechanical properties and morphological structure of an NC hydrogels. As well as to develop a stable hydrogels, the silicate nanoparticles must to be well dispersed in solvent system and to be control the large-scale structures. Based on these facts the silicates nanoparticles are incorporated into PAAm and PEO matrices to function as cross-linking agents and to improve network strength.

2.4.2 Poly(ethylene Oxide)–Silicate Nanocomposite Hydrogels

The impact of published work and trend in the NC hydrogels made up from PEO and silicate nanoparticles are well explained in this section. Among various clay silicate and polymers are available, but we focus on NC hydrogels from Laponite and PEO have been used as standard systems with which to study polymer–nanoparticle interactions and shear orientation. Laponite nanoparticles are synthetic one and plate-like poly-ions that uniformly disperse in water and behave like highly multifunctional cross-links agents to the PEO. The cross-linking is reversible for the reason that the polymer rapidly adsorbs and desorbs from the Laponite nanoparticle surfaces, but the exact interactions between silicate and the PEO are not clear until. However, many researchers recognize that ionic, hydrogen bonding, dipole and other interactions such as polymer entanglements should play a significant role when cross-linking to the silicate takes place. Nelson and Cosgrove (Nelson & Cosgrove, 2004a,b) suggest that PEO adsorbed onto Laponite particles to forms a dense layer of predominantly trains and loops on top of the nanoparticle and large loops around the edge of the particles (Figure 2.5a). The viscoelastic properties and structures of hydrogel can be adjusted through vary of parameters such as pH, temperature, ionic strength, and composition. For instance, by changing the PEO and Laponite compositions to produce different solutions such as shake gels, flowing gels or stable hydrogels that can be swollen in water (Can & Okay, 2005; Loizou *et al*., 2005; Loizou *et al*., 2010; Pozzo & Walker, 2004). The shear-induced gelation of shake gels is reversible and strongly vulnerable on the concentration, temperature, time and molecular weight of PEO (Can & Okay, 2005; Li *et al*., 2006). According to published research work on hydrogels in the literature, the shear deforms the large PEO–Laponite aggregates and displays new surface area to the formation of the latest polymer bridges, which quickly form a network that intervals the whole solution and forms a hydrogel. However, when the shaking was stops, thermal variations are enough in order to desorb the polymer from the nanoparticle and the hydrogel relaxes back to a fluid after some time. The applied shear is not huge enough in order to overcome the randomizing effects generated by the polymer and nanoparticle relaxations. The kinetics of hydrogel formation in Laponite–PEO dispersions of changing polymer molecular weight (Mw) was calculated by using rheology (Baghdadi *et al*., 2005). The hydrogel formation mechanisms were established to be time dependent and more attention will be needed in order to understand the exact mechanism. In addition, the same group was reported an alternate work showed a re-entrant activities from soft solid to liquid back to soft solid while the PEO molecular weight is increased (Baghdadi *et al*., 2008). On the other hand Daga and Wagner (2006) published their work on the viscoelastic and relaxation behavior of Laponite–PEO hydrogels over a range of concentrations. Time–concentration and time–temperature superposition were applied to produce rheological master curves. The addition of Laponite nanoparticles to a concentrated polymer solution enhanced the relaxation time, however, decreased the elastic modulus, which was recognized to the polymer adsorption and bridging. At high Laponite and polymer concentrations, Loizou *et al*. (2005) reported strong hydrogels with gum-like reliability. The polymer coated silicate nanoplatelets were established to be energetically tethered together in detached bundles that form fractal-like structures with 'pores' into the micrometer system. A skeleton-like structure on the nanometer and micrometer scale would explanation for the lack of flow in a hydrogel consisting of 95% mass fractions

of water. The cross-linking is physical (noncovalent) interactions due to dipole, ionic, hydrogen bonding and other interactions that attach the polymer chains to the nanoparticles. The cross-linking of hydrogels is reversible for the reason that under deformation, the polymer chains may attach to and detach from the silicate nanoparticles. The hydrogels generally shear thin, a property that composes some of them injectable through syringe. After cessation of shear, the macrostructure and rigidity of the hydrogel reclaim completely within span of seconds implying that self-healing properties (Loizou *et al*., 2006; Thakur & Kessler, 2015). The shear-induced microsized structures noticed by Lin-Gibson *et al*. (2004) are consistent with earlier studies on related systems which recognized temporary microscale heterogeneities that promote during shear and disappear ahead cessation of shear. Although in this case shear may induce the innovation of new structure, it is also achievable that previously existing structures may disappear. For example, de Bruyn *et al*. (2008) reported that the presence of microsized PEO–Laponite aggregates in hydrogels break up and disappear above a critical shear rate.

To outline the reviewed work indicates that the interactions between PEO and Laponite nanoparticles are strongly impact on shear rate which supplied to the complex behavior of these hydrogels. The soft, rubbery reliability and the flexibility in altering the mechanical properties compose these hydrogels possible candidates for several applications, particularly biomedical applications. However, very few applications have been describes notwithstanding the huge interest in basic research. Among these applications, Takahashi *et al*. (2005) reported that a modified PEO–Laponite hydrogel system can be fabricated into a controlled drug delivery system at physiological conditions. A wide variety of applications is introduced for colloidal dispersions (attractive hydrogels) prepared from nanoparticle bentonites (natural layered silicate) and PEO polymer. Sol–gel phase representation in water was clearly showed hydrogel boundaries as a function of composition; while it is not clear if these hydrogels has 3D (three dimensional) stable structures as necessary in hydrogels. The yield stress of the hydrogels and their sol–gel transitions are favorable properties in technical applications such as cosmetics, pharmaceuticals, oil well drilling, mortar and emulsions, shear thickening paints, antifriction agents and additives for concrete (Lagaly & Ziesmer, 2006). Further accurate spatial and orientational arrangements of nanoparticles within a hydrogel network can be attained through the use of block copolymers instead of homopolymers. The block copolymer hydrogel gives its liquid crystalline structure on the nanoparticles which do not self-assemble itself (Pozzo & Walker, 2007). For instance, NC hydrogels based on PEO–polypropylene oxide (PPO)–PEO block copolymers and spherical clay nanoparticles have been explored for the development of templated nanoparticle arrays (Pozzo & Walker, 2008). The isotropic to liquid crystalline phase transitions in Pluronic-type PEO–PPO–PEO hydrogels can be used to disperse and order silica nanoparticles on a nanometer length scale (Figure 2.5f) (Nelson & Cosgrove, 2005; Pozzo & Walker, 2007, 2008). Overall, observations of these block copolymer NC hydrogels can be intended to have sophisticated unique properties *via* self-assembly.

2.4.3 Poly(acryl Amide) and Poly(vinyl Alcohol)–Silicate-Based Nanocomposite Hydrogels

Hydrogels based on PAAm may indicates oversensitivity toward external stimuli such as pH, temperature, light, pressure, mechanic, solvent, electric, and magnetic fields

(Cho *et al*., 2008; Gorelikov *et al*., 2004; Haraguchi *et al*., 2006; Hou *et al*., 2008; Nayak & Lyon, 2004; Satarkar & Zach Hilt, 2008; Zhao *et al*., 2005). The chemical cross-linking of PAAm-based polymers with silicate nanoparticles (Montmorillonite, Laponite, Bentonite, etc.) leads to NC hydrogels accompanying a comprehensive properties that have fascinated to many scientists (Figure 2.5b). Unambiguously, the thermosensitive coil to globule transition and the lower critical solution temperature of PAAm polymers are of interest. The fabrication of hydrogels frequently requires the polymerization reaction to be initiated from the silicate results change in silicate surface to form brush-like surface structure, whereas the brush-like polymers grow longer and they intersect numerous silicate nanoparticles led to a cross-linked polymer network (Haraguchi *et al*., 2005; Zhu *et al*., 2006). Haraguchi and Li (2005, 2006) compared the structure of organically cross-linked hydrogels with Laponite silicate cross-linked poly(*N*-isopropyl acryl amide) (PNIPAAm) NC hydrogels. This group also revealed that the number of cross-linking units per space is about 700 times higher for the organically cross-linked hydrogels compared to the NC hydrogels. Organically cross-linked hydrogels with an extensive distribution of polymer chain lengths between the several cross-linking sites construct high localized stresses under distortion and fracture easily. However, NC hydrogels that has identical polymer chain lengths and a more uniform distribution of Laponite silicates cross-linkers bypass the localization of stress during distortion and expose the remarkable mechanical properties. Furthermore, the PAAm polymers chains are more flexible when compared to PNIPAAm polymer, which leads to dissimilarities in hysteresis, elastic recovery, tensile strength and elongation at break (Zhu *et al*., 2006). Spatial homogeneity can be deliberated thru scattering or optical transparency techniques. Nie *et al*. (2005, 2006) studied on hydrogel network structure, chain dynamics and degree of spatial in-homogeneity. It was resolved that the thermal variations of nanoparticles are widely suppressed by the network formation and that chain dynamics are more or less independent of the cross-linking agent. Overall observations of these studies recommend that the efficient functionality of the Laponite silicate cross-linkers is about 50 and that this high functionality as well as large correlation lengths produce the large-scale structures that lead to remarkable mechanical properties (Haraguchi & Li, 2005, 2006; Nie *et al*., 2005, 2006; Okay & Oppermann, 2007). Mu and Zheng (2007) adapted PNIPAAm hydrogels that were cross-linked with hydrophobic polyhedral oligomeric silsesquioxane (POSS). These hydrogels showed noticeable enhancement in the temperature swelling/de-swelling kinetics. In addition, the POSS cross-linkers improved the mechanical strength of the hydrogels, which in turn permitted to increase the number of swelling/de-swelling cycles without obvious degradation of the hydrogel. Thus swelling/de-swelling of the PNIPAAm–POSS hydrogel is much faster than PNIPAAm–Laponite hydrogels, nevertheless this enhancement is particularly authentic at high cross-linker concentrations (Zhang & Wang, 2007). A recent paper analyze the swelling behavior of PAAm hydrogels cross-linked with different silicates (montmorillonite, mica, attapulgite, kaolinite, and vermiculite) and the silicates drastically affects the swelling properties and thermal behavior of the hydrogel in addition to the polymerization reaction mechanism. Hence, the cross-linker selected should be based on the type of application of the hydrogel. For instance, a MMT cross-linker should be used for applications where a fast swelling rate is required; however, a mica cross-linker should be selected if the hydrogel prerequisites to swell/de-swell

multiple times (Zhang & Wang, 2007). For the support of above statement, Ziesmer and Stock (2008) reported on poly(vinylpyridine)–zeolite and PNIPAAm–zeolite NC hydrogels. Furthermore, they report the synthesis of core–shell structures with the usage of a microporous zeolite core material which are pH [poly(vinylpyridine)–zeolite] and temperature (PNIPAAm–zeolite) responsive, having strong potential in separation and controlled release applications. Apart from PAAms, other polymers such as PVA have been used for fabricating the various NC hydrogels. Adding MMT silicate nanoparticles to PVA can improve the mechanical performance of a hydrogel and they can be used in high shear applications (Kokabi *et al*., 2007). The addition of surfactant to PVA is generally applied results to change the interactions between polymer and silicate, as small amounts of surfactant increase the network strength of the hydrogel by strengthening the interaction between silicate and PVA. Further increase the surfactant concentration disorders the PVA–silicate binding, which in turn disorders the hydrogel network into a viscous solution (Liu & Hoffmann, 2004). Paranhos *et al.* (2007b) reported that the amount of MMT within a PVA–silicate hydrogel (up to 5%) increases the crystalline nature of PVA and decreases the pore size within the hydrogel network as well as decreases the mobility of PVA chains. However, addition of a second polymer (a sulfonated polyester) has an opposite effect on PVA leads to control the crystallinity in PVA–clay hydrogels (Paranhos *et al*., 2007a). The most recent applications of hydrogels are actuators, sensors and biomedical field. For example, Haraguchi *et al*. (2006) have employed the sensitivity toward external stimuli in order to fabricate silicate particles cross-linked PAAm and PNIPAAm hydrogels into smart drug delivery vehicles. The *in vivo* and *in vitro* antithrombogenicity, biocompatibility as well as the thermosensitivity of these soft materials are used as contact lenses (CLs) or implants in biomedical field. Furthermore, the mechanical durability is useful for development of elastic biomaterials such as artificial tendons and sutures. In another example, Matos *et al*. (2006) reported a spherical silicate nanoparticles doped PAAm hydrogels in order to increase the performance of biosensors through electro-osmotically improving the mass transfer of solutes over the hydrogel. Whereas electrophoresis does not drive neutral molecules and thus cannot be used for mass transfer augmentation, the internal pumping process developed by Matos *et al*. (2006) and reported a electro-osmotic flow nearby charged silicate nanoparticles surfaces which in return permits mass transfer of neutral molecules/solutes though hydrogels (Figure 2.5e). A quantitative theoretical interpretation of the experimental data by Matos *et al*. is presented by Hill (2007). Hill uses a mathematical model for the electro-osmotically boosted tracer flux association with an electro-kinetic model in order to determine the electro-osmotic pumping velocity from flux improvements (Hill, 2007).

2.5 Nanocomposite Hydrogels with Natural Polymers

Furthermore, we are also trying to disclosing the 'manmade hydrogels' from natural polymers and nanoparticles in this section. Although biological hydrogels appear to have near-infinite structural complexity hydrogels from natural polymers with no tertiary structure often have similar physical and chemical properties, most of which can be related to synthetic hydrogels (Kayitmazer *et al*., 2013). Natural polymers (chitosan,

starch, alginate, etc.) are used in NC hydrogels due to their unique properties such as biodegradability, biocompatibility, low cost, etc. A standard method (chemical modification of the biopolymer) is used to synthesis of natural polymer hydrogels in order to increase the polymer–nanoparticle interaction leads to form a mechanically stable hydrogel. Nevertheless, the chemical modification of biopolymers (the grafting of synthetic polymer or functional groups or onto the polymer) may alter the biocompatibility of the natural polymer due to the inadequate confiscation of toxic chemicals throughout the synthetic modification, which is a general cause for using unmodified natural polymers obtained from renewable resources. Unique method to encourage the gelation of natural polymers, suggested by Shchipunov *et al.* (2005) involves mineralization of the polymer (guar gum, chitosan, β-cyclodextrin, carboxymethylcellulose, etc.) with silica particles. In their work, water-soluble tetra kis (2-hydroxy ethyl) ortho silicate (THEOS) was dissolved along with the polymer. THEOS hydrolyzes *in situ* to yield silica nanoparticles which cross-link the polymer. The authors also report their procedure allows the gelation of a various group of then nongelable polysaccharides having anionic, cationic, linear, or branched regions. A more recent report describes the gelation of hydroxypropyl guar gum with THEOS and the release kinetics of a model drug loaded within the hydrogel matrix (Wang & Zhang, 2007). Stimuli-responsive NC hydrogels containing natural polymers obtained from renewable resources, like their synthetic polymer counterparts, have been studied for their response to changes in temperature and pH. Ma *et al.* (2007b) found that PNIPAAm-carboxymethyl chitosan IPNs cross-linked with Laponite silicate particles undergo similar phase transitions at ~33°C as PNIPAAm–clay hydrogels. However, the carboxymethyl chitosan containing hydrogel could absorb more water than the NC consisting of PNIPAAm-silicate when the pH was less than ~2.5 or greater than ~4. The authors further attributed to increase in swelling to the hydrophilicity of carboxymethyl chitosan. In addition, the chitosan-containing composite had a larger volume change with pH due to the amphoteric functional groups ($-NH_2$ and $-CH_2COOH$) present in the chitosan derivative. The same group found a similar trend with carboxymethyl cellulose-PNIPAAm semi-IPNs that were cross-linked with Laponite nanoparticles. In this case, the cellulose only having one ionizable functional group and displayed a peak in swelling ratio when the carboxylic acid groups (–COOH) are deprotonated (pH ~4.6) owing to electrostatic repulsions. Above this pH, sodium counter ions screen the electrostatic repulsions, while below this pH, hydrogen bonds form and reduce the swelling capacity (Ma *et al.*, 2007a).

2.6 Classifications of Hydrogels

Hydrogels are classified into several ways, depending on the development methods, sources, ionic charges, nature of swelling with changes in the environment, the nature of cross-linking or rate of biodegradation. A schematic classification of hydrogels is illustrated in Figure 2.7 (Hin; Ratner *et al.*, 2012). Among them, one of the important classifications is based on their cross-linking nature (Figure 2.4). The hydrogel network stability in their swollen state is owing to the presence of either physical or chemical cross-linking. Chemically cross-linked hydrogels are also known as permanent gels or

thermosetting hydrogels and they cannot be dissolved in any solvents unless the covalent cross-link points are cleaved. Furthermore, they cannot be reshaped through heat melting. They can be fabricating using any of these following methods:

- Copolymerization of hydrophilic monomers through cross-linkers.
- Water-soluble polymer segments through cross-linkers with di and/or multi-functional cross-linkers or using irradiation method (UV-vis, γ-irradiation, microwave, and electron beam).

The effectiveness of chemically cross-linked hydrogels is often inadequate due to lack of processability and post-process modifications, the shaping is carried out along with their polymerization reaction step. Furthermore, the cross-linking agents are used to development of hydrogels are highly toxic and the residues must be completely discarded before their use as biomaterials for various applications. In contrast, physically cross-linked hydrogels retain their physical stability owing to the presence of reversible physical connection related with chain entanglements, hydrophobic interaction, hydrogen bonding, crystallinity, and/or ionic complexation (Bae *et al*., 2000; Park & Bae, 2002; Qu *et al*., 2000). Physically cross-linked hydrogels are also known as temporary

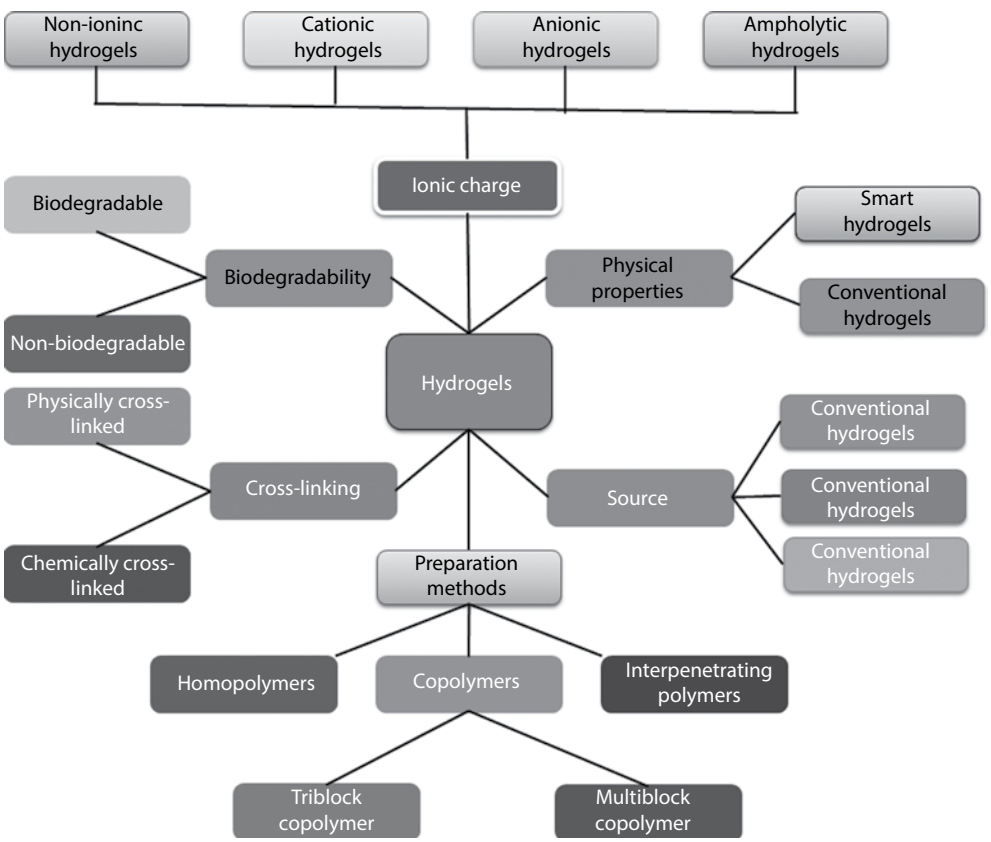

Figure 2.7 A schematic representation of hydrogel classifications.

or thermoplastic hydrogels. Swelling capacity of these hydrogels is probably dependent on the thermodynamic parameters such as pH, temperature, salt type, and/or ionic strength. Alterations in such parameters may increase or decrease their swelling ability. The presence of reversible cross-linking sites in physically cross-linked hydrogels allows solvent casting and/or thermal processing. In the development of these hydrogels, the use of toxic cross-linkers can also be omitted. Physically cross-linked hydrogels possess higher compressive strength compared with the corresponding chemically cross-linked hydrogels since the mechanical load can be more uniformly distributed through the crystallites of the three-dimensional structure (Devine & Higginbotham, 2003).

2.7 Applications of Hydrogels as Biomaterials

The objectives of this section to explain the hydrogels and its NC gels applications based on various previous research groups and discusses their practical issues. Certain significant properties of hydrogels and its NC gels for their applications as biomaterials are as follows according to Patel *et al.* (Alpesh & Kibret, 2011).

- Remarkable biocompatibility
- Robust oxygen permeability
- Low cell adhesion and protein adsorption
- Soft and tissue-like physical properties
- Marginal frictional irritation within the surrounding tissues on implantation
- Aqueous surface environment to protect cells and therapeutic drugs
- Microporous structure for additional transport channels
- Simplicity of surface modification with specific biomolecules
- Can be injected *in vivo* as a solution that gels at body temperature

The above properties of hydrogels made them ideal biomaterials for applications in cell encapsulation, drug delivery system, CLs and scaffolds for tissue engineering, intelligent cell culture substrates, wound dressing, biosensors, soft tissue replacement, and many more applications (Alpesh & Kibret, 2011; Fleige *et al.*, 2012).

2.7.1 Hydrogels for Drug Delivery Applications

Hydrogels and nanogels are frequently used more and more as nanovehicles for drug delivery (see Figure 2.8). As a common principle, the active delivery is either encapsulated/supramolecularly complexed and/or chemically conjugated with the nanocarrier hypothesis. When the delivery of a therapeutic species is used as nanocarriers determine novel medical effects depending on their structure, such as the capability to cross biological barriers and cellular membranes and interact with cell-surface receptors. Such medical effects are critically dependent on the nanoscale structure of these carriers and are translated to the drug or the genetic pay-load they contain (Moghimi *et al.*, 2001). The clear advantages provided by the nanocarrier mediated delivery of drugs, genes and diagnostic agents are mostly demonstrated by higher on-target accumulation,

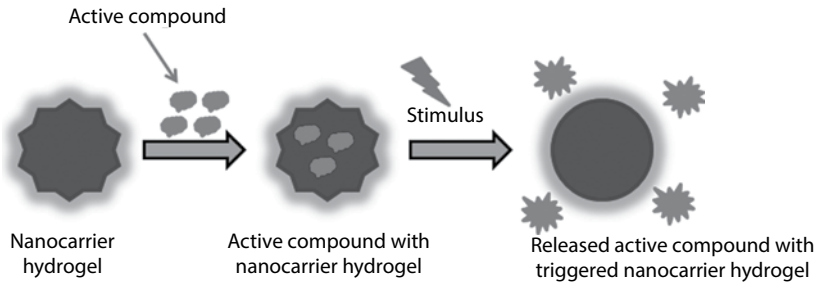

Figure 2.8 General scheme of a stimuli-responsive nanocarrier for the transport of active compounds.

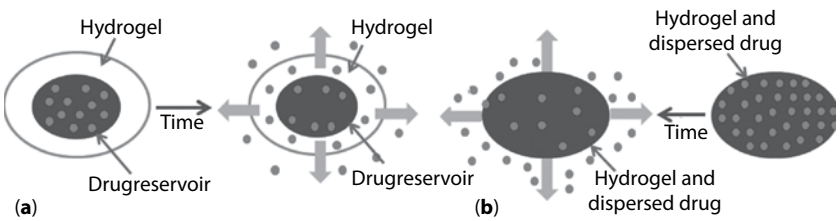

Figure 2.9 Scheme of drug release through a hydrogel membrane in a (a) reservoir system and (b) drug release from matrix systems.

up-regulated cellular intake and prolonged residence time of the active agents compared to substantially reduced off-target contact, instability and toxicity occurring with freely circulating low-molecular-weight therapeutics.

However, many patents and academic papers about possible applications of hydrogels in drug delivery have been published; nevertheless, hydrogels have attracted noticeable interest for their use in drug delivery due to their unique properties (Elvira *et al.*, 2002; Hoare & Kohane, 2008; Vashist *et al.*, 2014). The high porosity that characterizes hydrogels can easily be adjusted by controlling the density of cross-links in their matrix and the affinity to water. Their porous structure also allows drugs to be loaded and then released an active pharmaceutical ingredient over a long period (Hoare & Kohane, 2008). The drug can be loaded into a hydrogel and then its release may proceed through several mechanisms, such as diffusion controlled, swelling controlled, chemically controlled, and environmentally responsive release.

The diffusion controlled release technique can be represented by reservoir or matrix devices. Both allow the drug release by diffusion through the hydrogel mesh or the pores filled with water. A reservoir delivery (see Figure 2.9) system includes a drug-containing core coated with a hydrogel membrane, commonly available as capsules, cylinders, spheres or slabs. The concentration of the drug is higher in the center of the system to allow a constant release rate (Caló & Khutoryanskiy, 2015).

In swelling-controlled release devices the drug is dispersed within in a polymer matrix and when the polymer is in contact with a biofluid it starts swelling. The material then expands beyond its boundary allowing the diffusion of drug with the relaxation of polymer chains (Caló & Khutoryanskiy, 2015). This process is also called Case II transport and it shows constant, time-independent kinetics of release. It is known as 'anomalous transport', one that combines swelling-controlled release with diffusion

(Mathiowitz, 1999). The gradient existing between the dispersed drug in the hydrogel and the surrounding environment permits the diffusion of the active ingredient loaded from the high concentration through the hydrogel, to the lower one.

Chemically controlled release is used to describe molecule release determined by reactions happening inside the polymer matrix. The utmost usual reactions that happen within hydrogel systems are breakage of polymer chains *via* hydrolytic or enzymatic degradation or reversible or irreversible reactions happening between the polymer network and releasable drug. Under definite circumstances, the surface or bulk erosion of hydrogels will control the rate of drug release. Instead, if drug-binding molecules are incorporated in the hydrogels network, the binding equilibrium may regulate the drug release rate. Chemically controlled drug release can be advance categorized according to the type of chemical reaction occurring throughout the drug release step. Normally, the release of encapsulated or tethered drugs can occur through the degradation of pendant chains or during surface erosion or bulk degradation of the polymer backbone (Amsden, 1998; Kanjickal & Lopina, 2004; Peppas *et al*., 2000).

Eco-sensitive hydrogels have immense potential strength in numerous applications. Several environmental variables, such as elevated temperatures and low pH are found in the body and then used for site-specific controlled drug delivery. Hydrogels that are approachable to specific molecules, such as antigens or glucose, can be used as biosensors as well as drug delivery systems. Light-sensitive, pressure-responsive, and electrosensitive hydrogels also have the potential to be used in drug delivery and bioseparation. Whereas the concepts of these environment-sensitive hydrogels are sound, the practical applications require significant improvements in the hydrogel properties. The most important weakness of these external stimuli-sensitive hydrogels is due to their too low response time. Thus, fast-responsive hydrogels are needed and the uncomplicated method is attaining to develop a smaller and thinner hydrogels. This commonly makes the hydrogel systems too brittle and they possess poor mechanical strength in many applications. Environmentally sensitive hydrogels for drug delivery systems also need biocompatibility nature. Synthesis of novel polymer hydrogels and cross-linkers with more biocompatible and enhanced biodegradable properties would be necessary for various important applications, but it is very difficult task to have that properties. If the achievements of the past can be induced into the future, however, it is extremely possible that responsive hydrogels with a extensive range of desirable properties can be developed (Qiu & Park, 2001).

2.7.2 Hydrogels for Tissue-Engineering Scaffolds

Tissue-engineering intention is to replace the diseased or damaged tissues with implants that unacceptable repair and regeneration. Hydrogels and its NCs are promising materials for tissue engineering scaffolds. Tissue engineering has appeared as an innovative technology for the development of an ideal, responsive, living substitute with properties related to that of the natural tissue. Up to the present time, it has focused mainly on restoration, maintenance, and/or improvement of the functions of cartilage, bone, tendon, skin, ligament, blood vessels, and heart valves (Dunphy *et al*., 2014; Park *et al*., 2013; Rennerfeldt *et al*., 2013; Skaalure *et al*., 2014; Sudhakar *et al*., 2015; Yar *et al*., 2015; Zhang *et al*., 2015; Zhao *et al*., 2015). Scaffolds play a significant role in scaffold-guided *in vitro* tissue engineering and are basically 3D structural templates that support differentiation

and proliferation migration and cell adhesion provide regulation for neo-tissue formation. The selected scaffold material should be reproducible and biocompatible without any batch-property difference, with high porosity and well-organized interconnectivity. Hydrogels appeared as useful scaffolding biomaterials as they become look like native tissues. Furthermore, the aqueous environment allowed hydrogels mimics those of cells in the body. They are porous for nutrient and waste diffusion and as deliberated, they are usually considered to be biocompatible. Nevertheless, the opportunity of batch-to-batch dissimilarity is an issue with native hydrogels that can be resolved by using biologically modified synthetic hydrogels. Both natural and synthetic hydrogels are used as scaffolds for tissue engineering to repair tendon, cartilage, skin, ligament, blood vessels and heart valves (Drury & Mooney, 2003). Native hydrogels used as scaffolds are agarose, alginate, chitosan, collagen, fibrin, gelatin, and hyaluronic acid (Peppas *et al*., 2006), whereas synthetic hydrogels focused as scaffolds are polyurethanes, PE), PNIPAAm, PVA, poly(acrylic acid) (PAA), and poly(propylene furmarate-co-ethylene glycol).

2.7.3 Hydrogels for Contact Lens

The irritation/discomfort associated with the use of CLs is often related to the eyelid-lens friction. Although the use of such devices is widespread, the information about the influence of the lacrimal fluid biomolecules on the tribological behavior of the CLs hydrogels is scarce. 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 and focusing on CLs materials (since the hydrogels used in this study are intended for that application), the amount of proteins and lipids that deposit on their surfaces is of high clinical relevance. This is especially critical for long term use CLs, which can stay in the eye for up to 30 days without removal. In this type of devices the adsorption of biomolecules shall be minimized, since it may lead to the reduction of comfort and visual acuity and to the increase of potential inflammatory reactions (Jones *et al*., 2003; Soltys-Robitaille *et al*., 2001). Concerning the hydrogels properties/behavior, Mirejovsky *et al*. (1991) found that the water content of high water/ionic commercial lenses considerably dropped as consequence of the adsorption of proteins. This may modify the transport of substances through the hydrogels (e.g. oxygen permeability) and optical properties like the refractive index (Efron *et al*., 2007; González-Méijome *et al*., 2006). More recently, Lord *et al*. (2006) also observed that when lysozyme and cholesterol solutions contact hydrogels of poly(2-hydroxye thylmethacrylate) and methacrylic acid [P(HEMA-MAA)], changes in the hydrogel structure occur, with water being displaced. More recently, Silva *et al*. (2015) reported the effect of the presence of albumin and cholesterol in the lubricant medium, on the frictional response of two model hydrogels for CLs.

2.7.4 Hydrogels for Cell Encapsulation

Injectable hydrogel systems (IHS) that can gelate *in situ* upon administration have gained a lot of interest over the past few years (Jeong *et al*., 2002; Ruel-Gariépy & Leroux, 2004). These hydrogels are designed for direct administration into the body through simple injection delivery (Yu & Ding, 2008). Mostly, such hydrogel systems

are either cell-encapsulated or drug-loaded aqueous solutions that cross-link *in situ* at the site of defect (Yu & Ding, 2008). The hydrogel design principles of these injectable systems differ widely with their application and type of gelation employed. In addition, cell-encapsulated IHS should provide a stable, cell-adhesive environment to foster cell growth and tissue development. They should possess appreciable porosity, pore size and pore interconnectivity for effective diffusion of oxygen, nutrients, signaling molecules, and cellular waste. Furthermore, the HIS should match the modulus of the target tissue and possess material characteristics conducive for protein adsorption and extracellular matrix deposition. To date, various IHS have been widely investigated for cell encapsulation and delivery (Li *et al*., 2012; Patenaude *et al*., 2014; Seliktar, 2012; Yu & Ding, 2008). These hydrogels are either based on naturally derived polymers, such as hyaluronic acid (Tan *et al*., 2009), alginate (Endres *et al*., 2010), gelatin (Sakai *et al*., 2009), fibrin, or synthetic polymers (Li *et al*., 2012; Yu & Ding, 2008), based on PVA, polyethylene glycol (PEG), polylactones, and polypropylene fumarate. Recently, flexible elastomeric polymers based on polyols, which contain multiple hydroxyl (–OH) groups, have been reported for soft tissue applications (Bruggeman *et al*., 2010; Bruggeman *et al*., 2008; Yuan *et al*., 2013). These elastomers are composed of nontoxic monomers, which are endogenous to the body's metabolic cycle and possess rich OH functional groups that can be potentially utilized as sites for chemical modification or biofunctionalization (Bruggeman *et al*., 2010). Examples include poly(glycerol sebacate) elastomers, which have found use as scaffolds for nerve, vascular, myocardial, and cartilage tissue engineering, and xylitol-based polymers (Bruggeman *et al*., 2010), which have received considerable interest for their excellent elastic mechanical properties and enhanced biocompatibility, both *in vitro* and *in vivo*.

2.7.5 Artificial Muscles and Nerve Regeneration

Even from 1989, academics had understand the fabulous abilities of hydrogels to act as artificial muscles (Suzuki, 1989). A comprehensive review of artificial muscles, accepting that the muscle is both material and system have been recently prepared (Bassil *et al*., 2008). The authors state advantages of PAAm hydrogels for artificial muscles applications are as follows:

- Biocompatibility
- Low cost
- Properties and materials similar to living tissue
- Chemical manipulation of properties
- Adjustable shape

The primary drawback of hydrogels is slow response, which could not effectively use if we want to fast response, while to our knowledge there is no report on studies comparing the kinetics of artificial hydrogel muscles against actual muscles. In contrast to very few drug delivery methods are allows hydrogels as artificial muscles they should be made able to tolerate the physiological environment without degradation.

Hydrogels can be also well suit for nervous system repair due to unique properties. The central nervous system (CNS) contains of the brain and the spinal cord, although

the peripheral nervous system (PNS) connects CNS to apart human body. The noticeable difference between PNS and CNS is, while PNS can recover after damage, while the CNS has bounded ability of replacing lost or damaged neurons leads to permanent loss of function following a disease or accident. This difference has been attributed to the different environment in PNS and CNS lesion sites. Main barriers to regeneration are the glial scar, which is composed from reactive astrocytes and proteoglycans, degenerating myelin (myelin debris) and oligodendrocytes (Silver & Miller, 2004). Chondroitin sulfate proteoglycans are the primary inhibitory constituent of glial scars nevertheless their effect can be reduced or even eliminated with chondroitinase ABC (ChABC) (Busch & Silver, 2007). Moreover, the glial scar formation, CNS injury affect in cell death and pseudocyst creation further limiting regeneration. By promoting nerve growth factors and other therapeutic agents (such as ChABC) scholars are focusing on altering the environmental conditions in CNS lesion sites and thus restoring nerve regeneration capability. Hydrogels can also be used in spinal cord injury repair (Nisbet *et al*., 2008) by acting as scaffolds bridging the gap between lesions or by delivering neurotrophic factors (Jain *et al*., 2006) favoring regeneration of neural connections. Syková *et al*. (2006) report a good adhesion of HEMA hydrogels in the host tissue, bridging the whole spinal cord lesion site. Later, the same group observed a tiny pseudocyst mass in hydrogels network implanted one week after damage when compared to immediate implantation. Notwithstanding, when a solid hydrogel is implanted, the surgical process itself will cause damage. This damage could be provide by using liquid hydrogels solidifying inside the lesion site (Van Tomme *et al*., 2008). Jain *et al*. (2006) reported an agarose scaffold, gelling *in situ* and conformably filling an irregular spinal cord deficiency in adult rats. By embedding brain-derived neurotrophic factor (BDNF) releasing microtubules in the scaffold, neurite growth was effectively improved.

2.8 Conclusions

Hydrogels and its NCs have been used numerous applications from the last few decades owing to their unique swelling ability to the change of some parameter of the media. Hydrogels are appeared in biomedical areas particularly as scaffolds for tissue engineering and systems for gene delivery over 5 decades ago. Recently, hydrogels and its NC materials have received enormous interest for controlled delivery of therapeutic materials and direct specific biological activities. However, hydrogels have been fabricated as nanostructured systems, including basic water soluble chains in the form of particles in suspension and numerous materials have been also used for the synthesis nanostructured hydrogels. As biopolymeric materials, the use of cross-linked networks having biopolymers such as chitosan, alginate, carboxymethyl cellulose, lignin, carrageenan and hyaluronan or synthetic biodegradable macrochains such as PEO, poly(ε-caprolactone), poly(methyl-methacrylate), and PAA can be isolated. On the other hand, a few of synthetic polymeric materials, which are biocompatible but are not biodegradable, can also be interesting tools in the controlled delivery of active ingredients.

As per reviewing the nanostructured hydrogels preparation, numerous cross-linking methods can be used such as physical, chemical and irradiation cross-linking. In order

to developing a proper drug delivery system, we must carefully evaluate the hydrogel properties as well as physicochemical and pharmacokinetic properties of the active ingredient. The traditional drug delivery systems have draw backs such as the minimal synchronization between the required time for therapeutically effective drug plasma concentrations and the actual drug release profile exhibited by the dosage form. These limitations can be overcome by entrapping the drug into nanogel networks. As nanostructured hydrogels show a diversity of functional properties such as surface, swelling, permeation, mechanical, and optical properties, in addition to the unique property of undergoing unexpected volume changes from their swollen and collapsed states with respect to environmental stimuli, this unique feature of hydrogels can be effectively used to control the kinetics of drug release. From this viewpoint, different stimuli-sensitive hydrogels that respond to temperature or pH have been theoretically and experimentally reported owing these parameters are directly associated to the normal function of the human body. In summary, hydrogels and its nanostructured hydrogels are one of the most interesting nanoparticulate drug delivery systems due to their unique properties, which come together the characteristics of a hydrogel system with a nanoparticle. Hydrogels and its nanostructured hydrogels features are significant important for developing unique materials and to attain promising methods for controlled drug delivery, allowing the therapeutic effect of the active ingredient to be improved and to minimize the undesired effects.

Hydrogels and its nanostructured hydrogels are important classes of biomaterials with future attractive properties. This chapter highlighted some features of hydrogel properties and various applications. It is expected that hydrogels and its nanocomposites from renewable resources will continue to play significant roles in biomedical and biotechnological applications.

Acknowledgment

The author BM wishes to acknowledge the Tshwane University of Technology for their financial support.

References

Ahmed, E.M., Hydrogel: preparation, characterization, and applications: a review. *Journal of Advanced Research* 6, 105–121, 2015.

Mukesh, P., Kibret, M., Hydrogel Biomaterials, 2011.

Amsden, B., Solute diffusion within hydrogels. Mechanisms and models. *Macromolecules* 31, 8382–8395, 1998.

Bae, Y.H., Huh, K.M., Kim, Y., Park, K.-H., Biodegradable amphiphilic multiblock copolymers and their implications for biomedical applications. *Journal of Controlled Release* 64, 3–13, 2000.

Baghdadi, H., Jensen, E., Easwar, N., Bhatia, S., Evidence for re-entrant behavior in laponite–PEO systems. *Rheol Acta* 47, 121–127, 2008.

Baghdadi, H.A., Sardinha, H., Bhatia, S.R., Rheology and gelation kinetics in laponite dispersions containing poly(ethylene oxide). *Journal of Polymer Science Part B: Polymer Physics* 43, 233–240, 2005.

Barbucci, R., Consumi, M., Lamponi, S., Leone, G., Polysaccharides based hydrogels for biological applications. *Macromolecular Symposia* 204, 37–58, 2003.

Bassil, M., Davenas, J., El Tahchi, M., Electrochemical properties and actuation mechanisms of polyacrylamide hydrogel for artificial muscle application. *Sensors and Actuators B: Chemical* 134, 496–501, 2008.

Berger, J., Reist, M., Mayer, J.M., Felt, O., Peppas, N.A., Gurny, R., Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications. *European Journal of Pharmaceutics and Biopharmaceutics* 57, 19–34, 2004.

Bruggeman, J.P., Bettinger, C.J., Langer, R., Biodegradable xylitol-based elastomers: *in vivo* behavior and biocompatibility. *Journal of Biomedical Materials Research Part A* 95A, 92–104, 2010.

Bruggeman, J.P., Bettinger, C.J., Nijst, C.L.E., Kohane, D.S., Langer, R., Biodegradable xylitol-based polymers. *Advanced Materials* 20, 1922–1927, 2008.

Bryers, J.D., Giachelli, C.M., Ratner, B.D., Engineering biomaterials to integrate and heal: the biocompatibility paradigm shifts. *Biotechnology and Bioengineering* 109, 1898–1911, 2012.

Busch, S.A., Silver, J., The role of extracellular matrix in CNS regeneration. *Current Opinion in Neurobiology* 17, 120–127, 2007.

Caló, E., Khutoryanskiy, V.V., Biomedical applications of hydrogels: a review of patents and commercial products. *European Polymer Journal* 65, 252–267, 2015.

Calvert, P., Hydrogels for soft machines. *Advanced Materials* 21, 743–756, 2009.

Can, V., Okay, O., Shake gels based on Laponite–PEO mixtures: effect of polymer molecular weight. *Designed Monomers and Polymers* 8, 453–462, 2005.

Cho, E.C., Kim, J.-W., Fernández-Nieves, A., Weitz, D.A., Highly responsive hydrogel scaffolds formed by three-dimensional organization of microgel nanoparticles. *Nano Letters* 8, 168–172, 2008.

Coviello, T., Matricardi, P., Marianecci, C., Alhaique, F., Polysaccharide hydrogels for modified release formulations. *Journal of Controlled Release* 119, 5–24, 2007.

Čulin, J., Šmit, I., Andreis, M., Veksli, Z., Anžlovar, A., Žigon, M., Motional heterogeneity and phase separation of semi-interpenetrating networks and mixtures based on functionalised polyurethane and polymethacrylate prepolymers. *Polymer* 46, 89–99, 2005.

Daga, V., Wagner, N., Linear viscoelastic master curves of neat and laponite-filled poly(ethylene oxide)–water solutions. *Rheol Acta* 45, 813–824, 2006.

de Bruyn, J., Pignon, F., Tsabet, E., Magnin, A., Micron-scale origin of the shear-induced structure in Laponite–poly(ethylene oxide) dispersions. *Rheol Acta* 47, 63–73, 2008.

Devine, D.M., Higginbotham, C.L., The synthesis of a physically crosslinked NVP based hydrogel. *Polymer* 44, 7851–7860, 2003.

Drury, J.L., Mooney, D.J., Hydrogels for tissue engineering: scaffold design variables and applications. *Biomaterials* 24, 4337–4351, 2003.

Dunphy, S.E., Bratt, J.A.J., Akram, K.M., Forsyth, N.R., El Haj, A.J., Hydrogels for lung tissue engineering: biomechanical properties of thin collagen–elastin constructs. *Journal of the Mechanical Behavior of Biomedical Materials* 38, 251–259, 2014.

Ebringerová, A., Structural diversity and application potential of hemicelluloses. *Macromolecular Symposia* 232, 1–12, 2005.

Efron, N., Morgan, P.B., Cameron, I.D., Brennan, N.A., Goodwin, M., Oxygen permeability and water content of silicone hydrogel contact lens materials. *Optometry & Vision Science* 84, E328–E337, 2007.

Elvira, C., Mano, J.F., San Román, J., Reis, R.L., Starch-based biodegradable hydrogels with potential biomedical applications as drug delivery systems. *Biomaterials* 23, 1955–1966, 2002.

Endres, M., Wenda, N., Woehlecke, H., Neumann, K., Ringe, J., Erggelet, C., Lerche, D., Kaps, C., Microencapsulation and chondrogenic differentiation of human mesenchymal progenitor cells from subchondral bone marrow in Ca-alginate for cell injection. *Acta Biomaterialia* 6, 436–444, 2010.

Fleige, E., Quadir, M.A., Haag, R., Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: concepts and applications. *Advanced Drug Delivery Reviews* 64, 866–884, 2012.

Flory, P.J., Rehner, J., Statistical mechanics of cross-linked polymer networks II. Swelling. *The Journal of Chemical Physics* 11, 521–526, 1943.

Gong, J.P., Katsuyama, Y., Kurokawa, T., Osada, Y., Double-network hydrogels with extremely high mechanical strength. *Advanced Materials* 15, 1155–1158, 2003.

González-Méijome, J.M., Lira, M., López-Alemany, A., Almeida, J.B., Parafita, M.A., Refojo, M.F., Refractive index and equilibrium water content of conventional and silicone hydrogel contact lenses. *Ophthalmic and Physiological Optics* 26, 57–64, 2006.

Gorelikov, I., Field, L.M., Kumacheva, E., Hybrid microgels photoresponsive in the near-infrared spectral range. *Journal of the American Chemical Society* 126, 15938–15939, 2004.

Han, Y., Lee, E., Ji, B., Mechanical properties of semi-interpenetrating polymer network hydrogels based on poly(2-hydroxyethyl methacrylate) copolymer and chitosan. *Fibers and Polymers* 9, 393–399, 2008.

Haraguchi, K., Nanocomposite hydrogels. *Current Opinion in Solid State and Materials Science* 11, 47–54, 2007.

Haraguchi, K., Li, H.-J., Control of the coil-to-globule transition and ultrahigh mechanical properties of PNIPA in nanocomposite hydrogels. *Angewandte Chemie International Edition* 44, 6500–6504, 2005.

Haraguchi, K., Li, H.-J., Mechanical properties and structure of polymer–clay nanocomposite gels with high clay content. *Macromolecules* 39, 1898–1905, 2006.

Haraguchi, K., Li, H.-J., The effect of water content on the ultimate properties of rubbery nanocomposite gels. *Journal of Polymer Science Part B: Polymer Physics* 47, 2328–2340, 2009.

Haraguchi, K., Li, H.-J., Matsuda, K., Takehisa, T., Elliott, E., Mechanism of forming organic/inorganic network structures during *in-situ* free-radical polymerization in PNIPA–clay nanocomposite hydrogels. *Macromolecules* 38, 3482–3490, 2005.

Haraguchi, K., Takehisa, T., Nanocomposite hydrogels: a unique organic–inorganic network structure with extraordinary mechanical, optical, and swelling/deswelling properties. *Advanced Materials* 14, 1120–1124, 2002.

Haraguchi, K., Takehisa, T., Ebato, M., Control of cell cultivation and cell sheet detachment on the surface of polymer/clay nanocomposite hydrogels. *Biomacromolecules* 7, 3267–3275, 2006.

Haraguchi, K., Takehisa, T., Fan, S., Effects of clay content on the properties of nanocomposite hydrogels composed of poly(N-isopropylacrylamide) and clay. *Macromolecules* 35, 10162–10171, 2002.

Hill, R.J., Electric-field-enhanced transport in polyacrylamide hydrogel nanocomposites. *Journal of Colloid and Interface Science* 316, 635–644, 2007.

Hin, T.S., *Engineering Materials for Biomedical Applications*. World Scientific.

Hoare, T.R., Kohane, D.S., Hydrogels in drug delivery: progress and challenges. *Polymer* 49, 1993–2007, 2008.

Hou, Y., Matthews, A.R., Smitherman, A.M., Bulick, A.S., Hahn, M.S., Hou, H., Han, A., Grunlan, M.A., Thermoresponsive nanocomposite hydrogels with cell-releasing behavior. *Biomaterials* 29, 3175–3184, 2008.

Huang, T., Xu, H.G., Jiao, K.X., Zhu, L.P., Brown, H.R., Wang, H.L., A novel hydrogel with high mechanical strength: a macromolecular microsphere composite hydrogel. *Advanced Materials* 19, 1622–1626, 2007.

Jain, A., Kim, Y.-T., McKeon, R.J., Bellamkonda, R.V., *In situ* gelling hydrogels for conformal repair of spinal cord defects, and local delivery of BDNF after spinal cord injury. *Biomaterials* 27, 497–504, 2006.

Jeong, B., Kim, S.W., Bae, Y.H., Thermosensitive sol–gel reversible hydrogels. *Advanced Drug Delivery Reviews* 54, 37–51, 2002.

Jones, L., Senchyna, M., Glasier, M.-A., Schickler, J., Forbes, I., Louie, D., May, C., Lysozyme and lipid deposition on silicone hydrogel contact lens materials. *Eye & Contact Lens* 29, S75–S79, 2003.

Kadokawa, J.-i., Saitou, S., Shoda, S.-i., Preparation of polysaccharide–polymethacrylate hybrid materials by radical polymerization of cationic methacrylate monomer in the presence of anionic polysaccharide. *Polymers for Advanced Technologies* 18, 643–646, 2007.

Kanjickal, D.G., Lopina, S.T., Modeling of drug release from polymeric delivery systems – a review. *Critical Reviews in Therapeutic Drug Carrier Systems* 21, 345–386, 2004.

Kayitmazer, A.B., Seeman, D., Minsky, B.B., Dubin, P.L., Xu, Y., Protein-polyelectrolyte interactions. *Soft Matter* 9, 2553–2583, 2013.

Kokabi, M., Sirousazar, M., Hassan, Z.M., PVA–clay nanocomposite hydrogels for wound dressing. *European Polymer Journal* 43, 773–781, 2007.

Lagaly, G., Ziesmer, S., Sol–gel transitions of sodium montmorillonite dispersions by cationic end-capped poly(ethylene oxides) (surface modification of bentonites, IV). *Colloid and Polymer Science* 284, 947–956, 2006.

Lee, P.I., Absorbent polymer technology: Lisa Brannon-Peppas and Ronald S. Harland (Eds.), Elsevier Science Publishers B.V., Amsterdam, 1990, 278 pp. $107.75 or Dfl.210.00. *Journal of Controlled Release* 17, 297–298, 1991.

Li, J., Jiang, J., Li, C., Lin, M.Y., Schwarz, S.A., Rafailovich, M.H., Sokolov, J., Effect of temperature on shear-induced anisotropic structure in polymer clay hydrogels. *Macromolecular Rapid Communications* 27, 1787–1791, 2006.

Li, X., Xu, S., Wang, J., Chen, X., Feng, S., Structure and characterization of amphoteric semi-IPN hydrogel based on cationic starch. *Carbohydrate Polymers* 75, 688–693, 2009.

Li, Y., Huang, G., Zhang, X., Li, B., Chen, Y., Lu, T., Lu, T.J., Xu, F., Magnetic hydrogels and their potential biomedical applications. *Advanced Functional Materials* 23, 660–672, 2013.

Li, Y., Rodrigues, J., Tomas, H., Injectable and biodegradable hydrogels: gelation, biodegradation and biomedical applications. *Chemical Society Reviews* 41, 2193–2221, 2012.

Lin-Gibson, S., Kim, H., Schmidt, G., Han, C.C., Hobbie, E.K., Shear-induced structure in polymer–clay nanocomposite solutions. *Journal of Colloid and Interface Science* 274, 515–525, 2004.

Lin, C.-C., Metters, A.T., Hydrogels in controlled release formulations: network design and mathematical modeling. *Advanced Drug Delivery Reviews* 58, 1379–1408, 2006.

Liu, J., Hoffmann, H., Hydrogels in aqueous phases of polyvinylalcohol (PVA), surfactants and clay minerals. *Colloid Polym Sci* 283, 24–32, 2004.

Liu, T.-Y., Hu, S.-H., Liu, K.-H., Liu, D.-M., Chen, S.-Y., Study on controlled drug permeation of magnetic-sensitive ferrogels: effect of Fe3O4 and PVA. *Journal of Controlled Release* 126, 228–236, 2008.

Loizou, E., Butler, P., Porcar, L., Kesselman, E., Talmon, Y., Dundigalla, A., Schmidt, G., Large scale structures in nanocomposite hydrogels. *Macromolecules* 38, 2047–2049, 2005.

Loizou, E., Butler, P., Porcar, L., Schmidt, G., Dynamic responses in nanocomposite hydrogels. *Macromolecules* 39, 1614–1619, 2006.

Loizou, E., Porcar, L., Schexnailder, P., Schmidt, G., Butler, P., Shear-induced nanometer and micrometer structural responses in nanocomposite hydrogels. *Macromolecules* 43, 1041–1049, 2010.

Lord, M.S., Stenzel, M.H., Simmons, A., Milthorpe, B.K., The effect of charged groups on protein interactions with poly(HEMA) hydrogels. *Biomaterials* 27, 567–575, 2006.

Lovinger, A.J., Nano-, bio-, multi-, inter-, …: polymer research in an era of prefixes. *Journal of Macromolecular Science Part C* 45, 195–199, 2005.

Ma, J., Xu, Y., Fan, B., Liang, B., Preparation and characterization of sodium carboxymethylcellulose/poly(N-isopropylacrylamide)/clay semi-IPN nanocomposite hydrogels. *European Polymer Journal* 43, 2221–2228, 2007a.

Ma, J., Xu, Y., Zhang, Q., Zha, L., Liang, B., Preparation and characterization of pH- and temperature-responsive semi-IPN hydrogels of carboxymethyl chitosan with poly (N-isopropyl acrylamide) crosslinked by clay. *Colloid and Polymer Science* 285, 479–484, 2007b.

Mathiowitz, E., *Encyclopedia of Controlled Drug Delivery*. Wiley, 1999.

Mathur, A.M., Moorjani, S.K., Scranton, A.B., Methods for synthesis of hydrogel networks: a review. *Journal of Macromolecular Science Part C* 36, 405–430, 1996.

Matos, M.A., White, L.R., Tilton, R.D., Electroosmotically enhanced mass transfer through polyacrylamide gels. *Journal of Colloid and Interface Science* 300, 429–436, 2006.

Mirejovsky, D., Patel, A.S., Rodriguez, D.D., Effect of proteins on water and transport properties of various hydrogel contact lens materials. *Current Eye Research* 10, 187–196, 1991.

Miyazaki, S., Endo, H., Karino, T., Haraguchi, K., Shibayama, M., Gelation mechanism of poly(N-isopropylacrylamide)–clay nanocomposite gels. *Macromolecules* 40, 4287–4295, 2007.

Moghimi, S.M., Hunter, A.C., Murray, J.C., Long-circulating and target-specific nanoparticles: theory to practice. *Pharmacological Reviews* 53, 283–318, 2001.

Montoro, S.R., Medeiros, S.d.F., Alves, G.M., Chapter 10 - Nanostructured hydrogels, in: Thomas, S., Shanks, R., Chandrasekharakurup, S. (Eds.), *Nanostructured Polymer Blends*. William Andrew Publishing, Oxford, pp. 325–355, 2014.

Mu, J., Zheng, S., Poly(N-isopropylacrylamide) nanocrosslinked by polyhedral oligomeric silsesquioxane: temperature-responsive behavior of hydrogels. *Journal of Colloid and Interface Science* 307, 377–385, 2007.

Murali Mohan, Y., Lee, K., Premkumar, T., Geckeler, K.E., Hydrogel networks as nanoreactors: a novel approach to silver nanoparticles for antibacterial applications. *Polymer* 48, 158–164, 2007.

Myung, D., Waters, D., Wiseman, M., Duhamel, P.-E., Noolandi, J., Ta, C.N., Frank, C.W., Progress in the development of interpenetrating polymer network hydrogels. *Polymers for Advanced Technologies* 19, 647–657, 2008.

Nayak, S., Lyon, L.A., Photoinduced phase transitions in poly(N-isopropylacrylamide) microgels. *Chemistry of Materials* 16, 2623–2627, 2004.

Nelson, A., Cosgrove, T., Dynamic light scattering studies of poly(ethylene oxide) adsorbed on laponite: layer conformation and its effect on particle stability. *Langmuir* 20, 10382–10388, 2004a.

Nelson, A., Cosgrove, T., A small-angle neutron scattering study of adsorbed poly(ethylene oxide) on Laponite. *Langmuir* 20, 2298–2304, 2004b.

Nelson, A., Cosgrove, T., Small-angle neutron scattering study of adsorbed pluronic tri-block copolymers on Laponite. *Langmuir* 21, 9176–9182, 2005.

Nguyen, M.K., Lee, D.S., Injectable biodegradable hydrogels. *Macromolecular Bioscience* 10, 563–579, 2010.

Nie, J., Du, B., Oppermann, W., Swelling, elasticity, and spatial inhomogeneity of poly(N-isopropylacrylamide)/clay nanocomposite hydrogels. *Macromolecules* 38, 5729–5736, 2005.

Nie, J., Du, B., Oppermann, W., Dynamic fluctuations and spatial inhomogeneities in poly(N-isopropylacrylamide)/clay nanocomposite hydrogels studied by dynamic light scattering. *The Journal of Physical Chemistry B* 110, 11167–11175, 2006.

Nisbet, D.R., Crompton, K.E., Horne, M.K., Finkelstein, D.I., Forsythe, J.S., Neural tissue engineering of the CNS using hydrogels. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 87B, 251–263, 2008.

Okay, O., Oppermann, W., Polyacrylamide–clay nanocomposite hydrogels: rheological and light scattering characterization. *Macromolecules* 40, 3378–3387, 2007.

Omidian, H., Park, K., Hydrogels, in: Siepmann, J., Siegel, R.A., Rathbone, M.J. (Eds.), *Fundamentals and Applications of Controlled Release Drug Delivery*. Springer US, pp. 75–105, 2012.

Paranhos, C.M., Soares, B.G., Machado, J.C., Windmöller, D., Pessan, L.A., Microstructure and free volume evaluation of poly(vinyl alcohol) nanocomposite hydrogels. *European Polymer Journal* 43, 4882–4890, 2007a.

Paranhos, C.M., Soares, B.G., Oliveira, R.N., Pessan, L.A., Poly(vinyl alcohol)/clay-based nanocomposite hydrogels: swelling behavior and characterization. *Macromolecular Materials and Engineering* 292, 620–626, 2007b.

Park, H., Choi, B., Hu, J., Lee, M., Injectable chitosan hyaluronic acid hydrogels for cartilage tissue engineering. *Acta Biomaterialia* 9, 4779–4786, 2013.

Park, J.H., Bae, Y.H., Hydrogels based on poly(ethylene oxide) and poly(tetramethylene oxide) or poly(dimethyl siloxane): synthesis, characterization, *in vitro* protein adsorption and platelet adhesion. *Biomaterials* 23, 1797–1808, 2002.

Patenaude, M., Smeets, N.M.B., Hoare, T., Designing injectable, covalently cross-linked hydrogels for biomedical applications. *Macromolecular Rapid Communications* 35, 598–617, 2014.

Peppas, N.A., Bures, P., Leobandung, W., Ichikawa, H., Hydrogels in pharmaceutical formulations. *European Journal of Pharmaceutics and Biopharmaceutics* 50, 27–46, 2000.

Peppas, N.A., Hilt, J.Z., Khademhosseini, A., Langer, R., Hydrogels in biology and medicine: from molecular principles to bionanotechnology. *Advanced Materials* 18, 1345–1360, 2006.

Peppas, N.A., Moynihan, H.J., Lucht, L.M., The structure of highly crosslinked poly(2-hydroxyethyl methacrylate) hydrogels. *Journal of Biomedical Materials Research* 19, 397–411, 1985.

Pozzo, D.C., Walker, L.M., Reversible shear gelation of polymer-clay dispersions. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* 240, 187–198, 2004.

Pozzo, D.C., Walker, L.M., Shear orientation of nanoparticle arrays templated in a thermoreversible block copolymer micellar crystal. *Macromolecules* 40, 5801–5811, 2007.

Pozzo, D.C., Walker, L.M., Macroscopic alignment of nanoparticle arrays in soft crystals of cubic and cylindrical polymer micelles. *The European Physical Journal E* 26, 183–189, 2008.

Qiu, Y., Park, K., Environment-sensitive hydrogels for drug delivery. *Advanced Drug Delivery Reviews* 53, 321–339, 2001.

Qu, X., Wirsén, A., Albertsson, A.C., Novel pH-sensitive chitosan hydrogels: swelling behavior and states of water. *Polymer* 41, 4589–4598, 2000.

Ratner, B.D., Hoffman, A.S., Schoen, F.J., Lemons, J.E., *Biomaterials Science: An Introduction to Materials in Medicine*. Elsevier Science, 2012.

Rennerfeldt, D.A., Renth, A.N., Talata, Z., Gehrke, S.H., Detamore, M.S., Tuning mechanical performance of poly(ethylene glycol) and agarose interpenetrating network hydrogels for cartilage tissue engineering. *Biomaterials* 34, 8241–8257, 2013.

Ruel-Gariépy, E., Leroux, J.-C., *In situ*-forming hydrogels—review of temperature-sensitive systems. *European Journal of Pharmaceutics and Biopharmaceutics* 58, 409–426, 2004.

Sakai, S., Hirose, K., Taguchi, K., Ogushi, Y., Kawakami, K., An injectable, *in situ* enzymatically gellable, gelatin derivative for drug delivery and tissue engineering. *Biomaterials* 30, 3371–3377, 2009.

Satarkar, N.S., Hilt, J.Z., Magnetic hydrogel nanocomposites for remote controlled pulsatile drug release. *Journal of Controlled Release* 130, 246–251, 2008.

Satarkar, N.S., Zach Hilt, J., Hydrogel nanocomposites as remote-controlled biomaterials. *Acta Biomaterialia* 4, 11–16, 2008.

Schexnailder, P., Schmidt, G., Nanocomposite polymer hydrogels. *Colloid and Polymer Science* 287, 1–11, 2009.

Schoof, H., Apel, J., Heschel, I., Rau, G., Control of pore structure and size in freeze-dried collagen sponges. *Journal of Biomedical Materials Research* 58, 352–357, 2001.

Seliktar, D., Designing Cell-Compatible Hydrogels for Biomedical Applications. *Science* 336, 1124–1128, 2012.

Shchipunov, Y.A., Karpenko, T.y.Y., Krekoten, A.V., Postnova, I.V., Gelling of otherwise nongelable polysaccharides. *Journal of Colloid and Interface Science* 287, 373–378, 2005.

Silva, D., Fernandes, A.C., Nunes, T.G., Colaço, R., Serro, A.P., The effect of albumin and cholesterol on the biotribological behavior of hydrogels for contact lenses. *Acta Biomaterialia* 26, 184–194, 2015.

Silver, J., Miller, J.H., Regeneration beyond the glial scar. *Nature Reviews Neuroscience* 5, 146–156, 2004.

Skaalure, S.C., Dimson, S.O., Pennington, A.M., Bryant, S.J., Semi-interpenetrating networks of hyaluronic acid in degradable PEG hydrogels for cartilage tissue engineering. *Acta Biomaterialia* 10, 3409–3420, 2014.

Soltys-Robitaille, C.E., Ammon Jr, D.M., Valint Jr, P.L., Grobe Iii, G.L., The relationship between contact lens surface charge and *in-vitro* protein deposition levels. *Biomaterials* 22, 3257–3260, 2001.

Sudhakar, C.K., Upadhyay, N., Jain, A., Verma, A., Narayana Charyulu, R., Jain, S., Chapter 5 – Hydrogels—Promising Candidates for Tissue Engineering, in: Ninan, S.T.G. (Ed.), *Nanotechnology Applications for Tissue Engineering*. William Andrew Publishing, Oxford, pp. 77–94, 2015.

Suzuki, M., An artificial muscle by PVA hydrogel can generate high power close to living skeletal muscles, Engineering in Medicine and Biology Society, 1989. Images of the Twenty-First Century, Proceedings of the Annual International Conference of the IEEE Engineering in, pp. 916–917, vol. 913, 1989.

Syková, E., Jendelová, P., Urdzíková, L., Lesný, P., Hejčl, A., Bone marrow stem cells and polymer hydrogels—two strategies for spinal cord injury repair. *Cellular and Molecular Neurobiology* 26, 1111–1127, 2006.

Takahashi, T., Yamada, Y., Kataoka, K., Nagasaki, Y., Preparation of a novel PEG–clay hybrid as a DDS material: dispersion stability and sustained release profiles. *Journal of Controlled Release* 107, 408–416, 2005.

Tan, H., Ramirez, C.M., Miljkovic, N., Li, H., Rubin, J.P., Marra, K.G., Thermosensitive injectable hyaluronic acid hydrogel for adipose tissue engineering. *Biomaterials* 30, 6844–6853, 2009.

Tanaka, Y., Gong, J.P., Osada, Y., Novel hydrogels with excellent mechanical performance. *Progress in Polymer Science* 30, 1–9, 2005.

Thakur, V.K., Kessler, M.R., Self-healing polymer nanocomposite materials: a review. *Polymer* 69, 369–383, 2015.

Thakur, V.K., Thakur, M.K., Recent advances in green hydrogels from lignin: a review. *International Journal of Biological Macromolecules* 72, 834–847, 2015.

Thakur, V.K., Thakur, M.K., Recent advances in graft copolymerization and applications of chitosan: a review. *ACS Sustainable Chemistry & Engineering* 2, 2637–2652, 2014a.

Thakur, V.K., Thakur, M.K., Recent trends in hydrogels based on psyllium polysaccharide: a review. *Journal of Cleaner Production* 82, 1–15, 2014b.

Timell, T.E., Recent progress in the chemistry of wood hemicelluloses. *Wood Science and Technology* 1, 45–70, 1967.

Van Tomme, S.R., Storm, G., Hennink, W.E., *In situ* gelling hydrogels for pharmaceutical and biomedical applications. *International Journal of Pharmaceutics* 355, 1–18, 2008.

Vashist, A., Vashist, A., Gupta, Y.K., Ahmad, S., Recent advances in hydrogel based drug delivery systems for the human body. *Journal of Materials Chemistry B* 2, 147–166, 2014.

Wang, F., Li, Z., Khan, M., Tamama, K., Kuppusamy, P., Wagner, W.R., Sen, C.K., Guan, J., Injectable, rapid gelling and highly flexible hydrogel composites as growth factor and cell carriers. *Acta Biomaterialia* 6, 1978–1991, 2010.

Wang, G.-H., Zhang, L.-M., Manipulating formation and drug-release behavior of new sol–gel silica matrix by hydroxypropyl guar gum. *The Journal of Physical Chemistry B* 111, 10665–10670, 2007.

Weiss, R.G., Terech, P., *Molecular Gels: Materials with Self-Assembled Fibrillar Networks*. Springer, 2006.

Yar, M., Shahzad, S., Siddiqi, S.A., Mahmood, N., Rauf, A., Anwar, M.S., Chaudhry, A.A., Rehman, I.u., Triethyl orthoformate mediated a novel crosslinking method for the preparation of hydrogels for tissue engineering applications: characterization and *in vitro* cytocompatibility analysis. *Materials Science and Engineering: C* 56, 154–164, 2015.

Yasuda, K., Ping Gong, J., Katsuyama, Y., Nakayama, A., Tanabe, Y., Kondo, E., Ueno, M., Osada, Y., Biomechanical properties of high-toughness double network hydrogels. *Biomaterials* 26, 4468–4475, 2005.

Yu, L., Ding, J., Injectable hydrogels as unique biomedical materials. *Chemical Society Reviews* 37, 1473–1481, 2008.

Yuan, L., Wenchao, H., Wayne, D.C., Qizhi, C., A comparative study on poly(xylitol sebacate) and poly(glycerol sebacate): mechanical properties, biodegradation and cytocompatibility. *Biomedical Materials* 8, 035006, 2013.

Zhang, J., Wang, A., Study on superabsorbent composites. IX: Synthesis, characterization and swelling behaviors of polyacrylamide/clay composites based on various clays. *Reactive and Functional Polymers* 67, 737–745, 2007.

Zhang, X., Xu, B., Puperi, D.S., Yonezawa, A.L., Wu, Y., Tseng, H., Cuchiara, M.L., West, J.L., Grande-Allen, K.J., Integrating valve-inspired design features into poly(ethylene glycol) hydrogel scaffolds for heart valve tissue engineering. *Acta Biomaterialia* 14, 11–21, 2015.

Zhao, X., Ding, X., Deng, Z., Zheng, Z., Peng, Y., Long, X., Thermoswitchable electronic properties of a gold nanoparticle/hydrogel composite. *Macromolecular Rapid Communications* 26, 1784–1787, 2005.

Zhao, X., Irvine, S.A., Agrawal, A., Cao, Y., Lim, P.Q., Tan, S.Y., Venkatraman, S.S., 3D patterned substrates for bioartificial blood vessels – the effect of hydrogels on aligned cells on a biomaterial surface. *Acta Biomaterialia* 26, 159–168, 2015.

Zhu, M., Liu, Y., Sun, B., Zhang, W., Liu, X., Yu, H., Zhang, Y., Kuckling, D., Adler, H.-J.P., A novel highly resilient nanocomposite hydrogel with low hysteresis and ultrahigh elongation. *Macromolecular Rapid Communications* 27, 1023–1028, 2006.

Ziesmer, S., Stock, N., Synthesis of bifunctional core–shell particles with a porous zeolite core and a responsive polymeric shell. *Colloid Polym Sci* 286, 831–836, 2008.