Chapter 4
Crosslinked Polymer Hydrogels

Reem K. Farag and Salma Hani

Abstract The use of synthetic crosslinked polymer gels has increased in recent years, due to their unique characteristics such as high mechanical strength, service life and water and oil swelling, as well as being biocompatible. They have been studied as promising candidates in various fields such as cardiac and oil sobrieties, contact lenses, cosmetics, drug delivery, tissue engineering, wound dressing, among others. This chapter provides general information on polymer gels, including definition, classification, preparation methods and applications.

Keywords Gel applications · Hydrophilic polymer · Hydrophobic polymer · Swelling

4.1 Introduction

Polymers are macromolecules made from small parts called monomers linked to each other. The behavior of the polymer depends on several factors as inter- and intramolecular interactions such as van Deer Waals forces, hydrophobic association, electrostatic interactions and hydrogen bonds (Zhang et al. 2015a, b). However, the hydrophobic interactions and the hydrogen bonds result in an efficient polymer-polymer attraction which causes the association between polymers (Dai et al. 2015). Polymers can be divided into biopolymers and synthetic polymers. The biopolymers are macromolecules manufactured by the living organisms such as cellulose, DNA, peptides, proteins, etc. (Wang and Heilshorn 2015). These biopolymers are responsible in the organism for performing biological functions such as homeostasis and molecular motions. The synthetic polymers are chemical compounds that are man-made such as

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nylon, poly(acrylamide) (PAAm), poly(ethylene glycol) (PEG), poly(vinyl chloride) (PVC), etc., which are used in different industrial purposes (Chin et al. 2017).

Crosslinked polymer gels are three-dimensional (3D) hydrophilic polymeric structures that can absorb huge volumes of water and other biological fluids and can even preserve them under pressure sometimes (Tomadoni et al. 2019). In addition, they have a high-water content, and with physical properties such as high flexibility similar to soft tissues. Crosslinked polymers are made to tolerate strong chemicals or eventually be disintegrated and dissolved (Peppas et al. 2000). The dissolution process can be carried out by altering the environmental conditions such as ionization of the solution, pH or temperature (Shimba et al. 2017).

4.1.1 Crosslinking Process

Crosslinking is a process in polymer chemistry that results in a network structure that depends on a multidimensional extension of a chain polymer by a crosslink which is a bond that could be ionic or covalent that works by linking a polymer to other (Sun et al. 2018). This crosslinking process changes the liquid polymer to a gel or solid by restricting the movement capacity of the polymer chains individually, thus increasing the molecular weight (Mw) of the polymer (Lin et al. 2015; Gutiérrez and González 2017; Gutiérrez et al. 2016b; Gutiérrez et al. 2015a; Gutiérrez et al. 2016a; Gutiérrez et al. 2015b). The resulting crosslinked polymers have an essential elastic characteristic which gives the polymer the ability to stretch and return to its original structure. However, by increasing the number of crosslink, they become less elastic and could be prone to be fragile (Rosales et al. 2017). But, by using sulfur curing or vulcanization, depending on the insertion of short sulfur chains that work on bonding the polymer chains in the rubber can give it more strength and durability (Maitra and Shukla 2014), are also resistant to heat and wear, as well as being mechanically strong, non-soluble in aqueous fluids, since crosslinking form strong covalent bonds, which results in solvent insoluble materials. They can, however, absorb a larger solvent content, for this reason they are called gels (Billah et al. 2018). Crosslinking has been implemented to improve the mechanical strength, insolubility, rigidity and stiffness of polymers, thus allowing polymers to be considered potential candidates in various fields, including agricultural, biomedical, environmental and industrial (Griffith et al. 2018). Therefore, by controlling the type of crosslinker and the required concentration, promising crosslinked polymers with desired properties of pore size, thermal degradation, particle size and swelling are generated (Vining et al. 2019). There are two types of crosslinking which are chemical crosslinking, including (1) free-radical radiation, ultraviolet-visible (UV) radiation, condensation and (2) polymerization of small molecules, in addition to the physical and biological crosslinking (Feng et al. 2016).

4.1.2 *Forms of Crosslinked Polymers*

Over the last two decades, natural and synthetic crosslinked polymers have been potentially used in several applications, since both types have advantages and disadvantages (Fortman et al. 2018). The natural polymers have low thermal stability, more solubility and no strength, so in order to improve these characteristics it is necessary (Gong et al. 2016). Crosslinking processes are classified into two types: the *in-situ* crosslinking and the post-crosslinking (Akhtar et al. 2016). In order to synthesize the *in-situ* hydrogels, there are two methods: the first method depends on the polymerization of the small molecules in the presence of crosslinkers and initiators (Desai et al. 2015), while the second method depends on the direct crosslinking of the monomers, either naturally or synthetically, to obtain a polymer chain (Takashima et al. 2017). In general, the synthetic polymers are hydrophobic and tougher compared to natural polymers, which results in high durability in hydrogels, but slow degradation (Foster et al. 2015). However, the post-crosslinking process depends on crosslinking after polymerization (Akhtar et al. 2016).

Crosslinked polymers are categorized into different types based on several parameters, such as ionic charge, mechanical and structural properties and preparation method (Slaughter et al. 2009). According to the crosslinking mechanisms, the crosslinked polymers can be divided into three types: the chemical, biological and physical crosslinked polymers (Pakulska et al. 2015). The crosslinking of the polymers may be reversible or irreversible with respect to the nature of the crosslinking (Ghobril and Grinstaff 2015). The chemical method produces irreversible polymers. However, physical and biological methods lead to reversible crosslinked polymers through the application of electricity, light, magnetic field, pH change, pressure or stress (Sawada et al. 2019).

4.1.2.1 Physically Crosslinked Polymers

The physical crosslinked polymers are crosslinked by physical forces such as electrostatic forces, hydrogen bonds and hydrophobic interactions (Nystrom et al. 1996). This type of hydrogels can form reversible stable 3D gel structures from polymer solutions, and this occurs by changing some external stimulus such as concentration, ionic strength, pH and temperature (Hennink and Van nostrum 2012). According to Kjoniksen et al. (1998), an example of this hydrogels is the ethyl hydroxyl ethyl cellulose (EHEC) in the existence of an ionic surfactant which forms a thermo reversible gel at elevated temperatures.

4.1.2.2 Chemically Crosslinked Polymers

The chemically crosslinked polymers are also known as continuous or chemical gels. They are responsible for primary forces such as covalent bonding through chemical reactions in order to achieve the crosslinking of the macromolecules in solution (Wang and Heilshorn 2015). They are efficient to obtain and have high mechanical strength and heat resistance. When the chemical crosslinked polymers form a covalent bond, a permanent 3D network is formed. An example of these polymers are hydrogels made from HEC in the presence of a divinyl sulfone crosslinker (Ouyang et al. 2016). Two common methods are used for preparing chemically crosslinked polymers: the first method is the 3D polymerization which depends on the polymerization of hydrophilic molecules as vinyl monomers in the presence of multifunctional crosslinkers (Cao et al. 2015). However, the drawback of this method is the significant amount of the unreacted monomers which can be toxic and require extensive purification methods (Wu et al. 2018). The second method depends on the direct crosslinking of the hydrophilic polymers so that extensive purification procedures could be avoided due to the small available amounts of the toxic molecules in the system (Mahou et al. 2015). Polymers that are water soluble, including PAAm, PEG, poly(vinyl alcohol) (PVA) and polysaccharides are the main systems used for applications in the biomedical and pharmaceutical fields, due to their biocompatibility and non-toxicity (Caló and Khutoryanskiy 2015).

4.1.2.3 Biological Crosslinked Polymers

The biological crosslinking method is an evolving technique that depends on the use of biomolecules to achieve the crosslinking, such as opposite charged peptides, complementary oligonucleotides, in addition to heparin growth factors (Sadtler et al. 2019). While, the opposite charged peptides and the polymers can form connections that allow the formation of the biological crosslink (Contessi et al. 2019). In addition, this method aids the polymer is not solubilized in organic solvents or aqueous solutions. However, this type of crosslinking is perceived as not strong enough as the chemical crosslinking techniques (Chaudhuri et al. 2016).

4.2 Methods of Synthesis of Crosslinked Polymers

Several different strategies for crosslinking the polymers can be used depending on the nature of the polymer, which could be through the polymerization of the small molecules by condensation or by forming a covalent bond between the polymeric chains through the irradiation, which is done by using high-energy ionizing radiation, such as electron beam, and gamma and X-ray (Hassan and Peppas 2000). However, the gamma irradiation is considered more economical, since it uses low doses about 80 kGy and less for large parts that have high density, while for small parts the electron beam is mainly used such as in the production of cables and wires (Maitra and Shukla 2014). It could also be through the vulcanization of sulfur which depend on chemical reactions by introducing different chemicals accompanied by heating and, in some cases, with pressure. Thus, in all the cases, the chemical structure of the polymer will be altered during the crosslinking process.

Conventional polymerization techniques, such as the condensation and the free-radical polymerizations, are mainly used for chemically crosslinked polymers (Das et al. 2018). These techniques produce a degradable or a non-degradable crosslinked polymer which depends on the formation of the bond (Li et al. 2017). In addition, the crosslinked polymers that could be obtained from these techniques do not impose any difficulty during their application, i.e. due to their robust crosslinking ability provided by the primary forces, while crosslinked polymers that are achieved by physical crosslinking can cause some difficulties throughout its application due to its fragile crosslinking provided by secondary forces (Li et al. 2016). For this reason, chemical crosslinking is more preferred.

4.2.1 Free-Radical Polymerization

Free radical polymerization is one of the most widely used synthetic methods worldwide to produce crosslinked polymers, both by academics and industrialists. It is used to generate a substantial amount of the crosslinked polymers produced globally, comprising 45% of the industrial synthetic plastics and 40% of the manufactured rubber, which is equivalent to an amount of 100 and 4.6 million tons, respectively (Kade and Tirrell 2014). It is widely used due to the favorable properties provided over other polymerization methods. First, it is found to be highly reactive, which results in crosslinked polymers of high Mws and ‘crosslinking density’ (Pan et al. 2015). Second, this method supports several functional groups and takes place in soft environments (Lansalot et al. 2016). It is thus considered an effortless approach to the synthesis of crosslinking polymers. Free-radical polymerization is carried out in the existence of an initiator and heat. Mainly, acrylic acids and small acrylate-based molecules are synthesized and polymerized using this method. Free radical polymerization is further categorized as homopolymer, copolymer, semi-interpenetrating network and interpenetrating network (Sutirman et al. 2016). The homopolymers are crosslinked polymers of a type of hydrophilic small molecules units, while the copolymers are the result of crosslinking between two different monomers, where at least one is hydrophilic in order to be swellable. The interpenetrating and the semi-interpenetrating networks are produced due to the formation of a swelling network first and then to the formation of a second intermeshing network system.

4.2.1.1 Homopolymer

It refers to the polymer network that originates from the polymerization of a single monomer species in the presence of a crosslinker and an initiator. Crosslinked homopolymers are used in various applications such as contact lenses and drug delivery systems. For example, homopolymerization of *N*-acryloylglycinamide through free radical polymerization using the initiator 2,2′-azobisisobutyronitrile (AIBN) and the crosslinker *N*,*N*′-methylenebisacrylamide (MBAm), produced a hydrogel (Liu et al. 2014). *N*-vinyl-2-pyrrolidone can also be homopolymerized in the presence of a radical initiator AIBN and a crosslinker MBAm to create a pH-responsive hydrogel for the *in vitro* delivery of propranolol hydrochloride (Shantha and Harding 2002).

4.2.1.2 Copolymer

The copolymers are crosslinked polymers that are synthesized by polymerization of at least two different monomers with somewhere around a hydrophilic compound. Depending on the structure of the polymer chain, the copolymers are categorized into block, random and alternating copolymers. According to Zhou et al. (2016) a recent report portrays the synthesis of pH-temperature double stimuli-responsive hydrogel for medication drug release. In this study, PEG was reacted with methyl ether methacrylate to achieve methacrylate ended PEG, which copolymerized with *N*,*N*′-dimethylaminoethyl methacrylate. The solution of the copolymer was then mixed with α-cyclodextrin (α-CD) to form a pH-thermo double touch hydrogel, thus allowing the arrival of a model drug 5-fluorouracil to be adequately controlled by pH and temperature (Bi and Liang 2016).

4.2.1.3 Semi-Inter Penetrating Network (Semi-IPN)

It refers to a crosslinked polymer generated from the combination of two independent synthetic or natural polymer compounds, comprised in the form of a network. In addition, in the semi-IPN polymer, one of the compounds is usually a crosslinked polymer, while the other is a non-crosslinked polymer (Zhang et al. 2009). Due to the absence of the restricting interpenetrating elastic network, the semi-IPNs can effectively reserve fast kinetic response rates to pH or temperature, while offering the advantages as modified pore size and slow drug release.

4.2.1.4 Interpenetrating Polymer Systems (IPNs)

It refers to the combination of two polymers or more of which are synthesized immediately in the presence of the other polymer (Muniz and Geuskens 2001). This is achieved by the immersing a pre-polymerized crosslinked polymer in a solution of small molecules and an initiator. This method can overcome the thermodynamic incompatibility due to the permanent interlocking of the networks, which causes the structure stable (Zhang and Zhuo 2000). The main advantages of this polymer networks are that dense crosslinked polymers can be produced which are characterized to have a robust mechanical strength, and is more competent for drug delivery compared to the conventional gels. IPN’s pore sizes and the surface chemistry can be controlled in order to tune the drug release (Yin et al. 2007). IPNs can also moderate the effect of environmental changes on the crosslinked polymers, thus minimizing the drug burst release during oral delivery, due to their ability to prevent the swelling of the interpenetrating phases with respect to the elasticity (Rana et al. 2015).

4.2.2 Condensation Polymerization

Condensation polymers are identified as any type of polymers formed through the condensation reaction by the combination of small molecules, and obtaining water or methanol as byproducts (Kumru et al. 2017). Condensation polymerization is used to produce some of the main polymers, such as poly(amide)s, poly(carbonate)s and poly(ester)s. It also plays a special role in the history of polymer science, while the first genuinely synthetic polymer, Bakelite, was developed in 1907, as a condensation product of phenol and formaldehyde (Kade and Tirrell 2014). The polymers produced by this method can be degradable or non-degradable depending on the groups formed during the polymerization process (Kabiri et al. 2011). This polymerization method is performed in the existence of heat, catalyst or both. In addition, the polymers resulting from this method generally have low Mw (Wang et al. 2018a, b). The polymerizations are divided into two groups, which are the condensation and the addition, while a step growth method with the condensation polymerization has also been used by Song et al. (2016). However, not all condensation reactions use a step growth method. Nonetheless, the step growth mechanism is still considered the most widely used method for the condensation of polymers for materials of industrial importance (Jain et al. 2016).

4.2.3 Bulk Polymerization

This technique of polymerization generates crosslinked polymers by using one or more types of monomers (Wu et al. 2018). This variety of the types of monomers permits the production of crosslinked polymers with the desired properties for different applications. This technique typically requires the addition of a small amount of a crosslinking agent during the polymer production. The polymerization of the monomers is usually initiated with the help of chemical catalysts or UV radiation. In addition, the choice of the main initiator depends on the types of solvents and monomers that is used. The resulting crosslinked polymer can be generated in various forms comprising emulsions, films, membranes, particles or rods.

4.2.4 Ultraviolet (UV) Radiation

UV radiation is considered an economical route to achieve a crosslinked polymer compared to condensation and free radical polymerization techniques. In addition, the polymerization of the crosslinked polymer through this technique is perceived as safe, it also has the least amount of effect on the properties of the crosslinked polymer and does not require the addition of any chemical compound such as initiators, solvents and surfactants. Thus, it allows the crosslinked polymer to retain its proper swelling, mechanical strength and biocompatibility properties (Wang et al. 2016).

4.3 Properties of Crosslinked Polymers

Much of the crosslinked polymer chains are chemically or physically linked, and therefore, are considered as a molecule, regardless of size. For this reason, the Mw of the crosslinked polymer is not perceived and are occasionally called macromolecules or infinitely large molecules (Niu et al. 2019). Minor changes in environmental conditions can cause reversible and fast alterations in the crosslinked polymers. The changes in the environmental parameters, including electrical signal, enzyme presence, pH or temperature, can cause a change to the physical structure of the crosslinked polymers (Rao et al. 2016). The changes that are produced can take place at macroscopic levels, since they change the size and water content of the crosslinked polymer (Deng et al. 2011). The alteration in the ion concentrations inside the crosslinked polymer in relation to the external solution could change, the pH and the volume of the solvent. In addition, the response of the crosslinked polymers with acidic or basic functional groups to the external environment depends on the degree of ionization of the functional group (Rana et al. 2015).

4.3.1 Biocompatibility

Crosslinked polymers to be used in various applications in the biomedical field must be biocompatible and non-toxic. For this reason, before being applied the crosslinked hydrogels must pass the cytotoxicity and *in-vivo* toxicity tests in order to be applied (Nawaz et al. 2018). The biocompatibility is the ability of the material to respond appropriately in the host during a specific application. In addition, biocompatibility consists of two basic elements: biosafety and biofunctionality (Kirschning et al. 2018). The biosafety is the performance of an adequate response from the host with the absence of carcinogens, cytotoxicity and mutagenesis. However, it is not only based on the systemic response but also on the local response of the neighboring tissues (Ibáñez-Fonseca et al. 2018), while the biofunctionality is the polymer's ability to perform the intended and required tasks. This is mainly important for tissue engineering, since the nature of tissue construction is to continuously interact with the body through cell regeneration and healing processes (Szafulera et al. 2018). However, if the requirements are not met, this means that the gel could be fouled or that there are injuries and scars to the connected tissues (Molpeceres et al. 2018). In addition, the toxic chemicals such as emulsifiers, initiators, solvents, stabilizers and unreacted monomers that are used in the polymerization of the synthesis of crosslinked polymers could interact with the body if the conversion is not performed 100% correctly. This presents a challenge for biocompatibility *in vivo*. These chemicals are toxic to host cells if they are filtered to encapsulated cells or tissues (Choi et al. 2015).

4.3.2 *Degree of Crosslinking (DC)*

The DC of the polymers is often measured using the swelling experiment, where the crosslinked terpolymer sample is placed in a solvent which is usually water at suitable temperature conditions (Nam et al. 2016). The DC is assessed by measuring the changes that occur in the mass or the volume of the crosslinked polymer. It should be noted that more crosslinked hydrogels have less swelling capacity. The DC will be calculated according to Flory (1953), where the sample is weighed dry then placed in the solvent for 24 hours and subsequently weighed at different time intervals.

4.3.3 *Mechanical Properties*

The mechanical properties of crosslinked polymers vary and can be tailored depending on the nature of the material. To achieve a gel with a higher toughness, the DC could be increased (Najdahmadi et al. 2018). A stronger gel can be acquired by increasing the DC, while decreasing the DC leads to a more brittle gel structure. The mechanical properties of crosslinked polymers have a great role in the biomedical and pharmaceutical fields, as they can be used for tendon and ligament repair, as well as they could be used as a matrix for the delivery of drugs, tissue engineering, and cartilage replacement and wound dressing material (Ahmadi et al. 2015; Chai et al. 2017). It is worth noting that crosslinked polymers can maintain their physical texture during the delivery of therapeutic medications (Benjamin 2017).

4.3.4 *Swelling Characteristics*

Crosslinked polymers are networks that can be swollen in a fluid medium. The liquids that are absorbed functions as a selective medium or filter to allow the entry of some solute molecules, while the network of polymers act as a matrix that holds the liquid together (Bukhari et al. 2015). Crosslinked polymers can contain up to a thousand times of their weight in liquids (Wang et al. 2018a, b). The nature of the water in the polymer can establish a complete infiltration of the nutrients into and the cell products out of the gel. When a dry crosslinked polymer absorbs water, the first molecules of water move towards the matrix working to hydrate the most polar hydrophilic groups. Since the polar groups are primarily linked, these results cause swelling of polymer bonds, exposing the hydrophobic groups, which also interact with the water molecules, which leads to secondary water binding. As a result, the network absorbs additional water due to the osmotic driving force of the network system to be diluted (Wang et al. 2018a, b). This swelling is opposed by the covalent or physical crosslinking, thus generating an elastic network withdrawal force.

Finally, the crosslinked polymer reaches the swelling equilibrium level. The extra water that is absorbed after the saturation of the polar and the hydrophobic groups will be defined as bulk water and acts as a filling to the space between the network chains and the pores (Zhu et al. 2019). Gradually, as the swelling of the networks increases, if the crosslinks are degradable, the gel will begin to dissolve at rates that depend on its structure (Chen et al. 2018).

4.4 Application of Crosslinked Polymers

4.4.1 Anti-Biological Crosslinked Polymers

Infections caused by pathogenic organisms such as bacteria, parasites and viruses are a major health problem despite the expansion in the medical field and health care. Conventional techniques for the treatment of the microbial agent as antibiotics usually lead to the development of resistance to the antibiotics (Anjum et al. 2016). Recent studies have found a new method to treat the microbial agents by using the anti-biological crosslinked polymers (Jones et al. 2015). The crosslinked polymers work on the rupture of the cell membranes of the microbial agent, resulting in the leakage of the cytoplasmic content and cell death (Tian et al. 2018). Several types of anti-biological crosslinked polymers have been developed in the recent years (Konwar et al. 2016). According to Echazú et al. (2017), crosslinked polymers based on chitosan containing varying concentrations of benzoyl have demonstrated high antibacterial and antifungal activity. The elevation of antimicrobial activity was associated with the increase in crosslinking concentration. Some researchers have also produced cellulose-based crosslinked polymers exhibiting high biocompatibility, mechanical strength, swelling property and antimicrobial activity against *Saccharomyces cervisiae*, thus showing the possibility of using crosslinked polymers as an antimicrobial candidate (Nordström and Malmsten 2017; Hu et al. 2018). It has also been reported that crosslinked polymers based on peptides show a significant antibacterial effect. In this sense, Rinehart et al. (2016), reported the development of a β-hairpin crosslinked polymer that had an anti-biological effect. Although the anti-biological crosslinked polymers have demonstrated remarkable activity against microbes. However, it was found that the interaction between the polymer and the cell membrane was nonspecific, thus causing in most cases the death of the mammalian cells (Picone et al. 2019). The solution that was proposed in order to use the crosslinked polymer as an antimicrobial agent, was to combine the crosslinked polymer with the antibiotics, in order to decrease the associated toxicity (Gallagher et al. 2016). Some researchers have also proposed another type of NP-loaded composite polymers which could be used in various applications such as wound dressing and against microbes (Mishra et al. 2018).

4.4.2 Artificial Muscles

The first generation of the crosslinked polymer has been used to mimic the neuromuscular and neurosensory systems (Miyamae et al. 2015). The muscles work by converting chemical reactions into mechanical actions. The artificial muscles that have been generated form the crosslinked polymers are comprised of an elastomer layer present between two layers of crosslinked polymers, while the elastomer layer acts as a di-electric, while the crosslinked polymer layers behave as a conductor (Iwaso et al. 2016). Metallic cables are used in order to connect the two layers of the crosslinked polymer to a power source. Upon the application of the voltage, the mobile electrons in the metal and the mobile ions present in the crosslinked polymer will move away or approach each other (Chandler 2018). Furthermore, accumulation of the mobile ions occurs between the elastomer and the polymer, simultaneously (Shi et al. 2016). In addition, due to the opposite polarities of the crosslinked polymers and the elastomer layers, this leads to a reduction in the thickness and an elevation in the elastomer layer. However, this could be avoided by generating a softer crosslinked polymer to prevent the deformation of the elastomer layer (Lee et al. 2016). Different designs of the artificial muscles could be generated depending on the electromechanical coupling which is based on the geometry of the layers (Fig. 4.1) (Dicker et al. 2017).

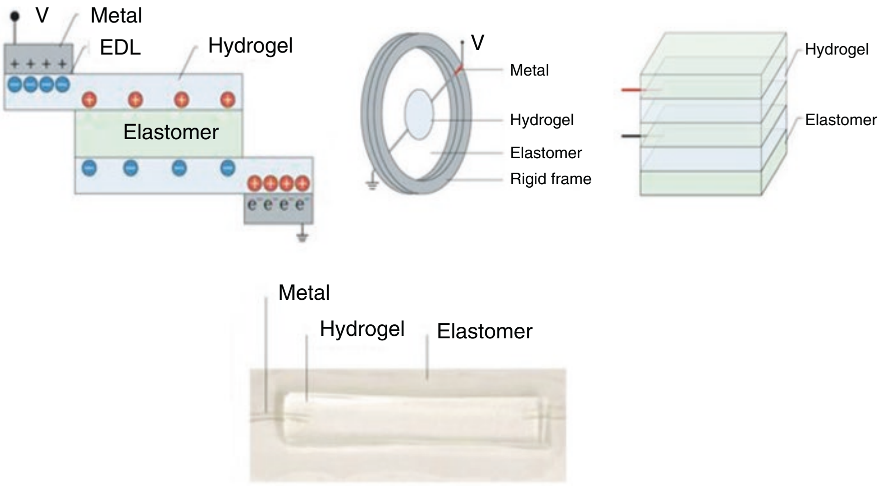

Fig. 4.1 Crosslinked polymer hydrogels for artificial muscle applications. Adapted with permission from Yang and Suo (2018)

4.4.3 Cancer Research

Crosslinked polymers have been implemented in many applications, including the cancer research (Song et al. 2015). Although most drugs are hydrophobic and this reduces their efficacy to be loaded and released from a crosslinked polymer (Pires et al. 2018). Two solutions to improve the release and loading of the drug from the polymer have been proposed, which are introducing a hydrophobic compound into the crosslinked polymer and incorporating nanoparticles (NP) which will act as an encapsulation for the hydrophobic domain (Norouzi et al. 2016). Recent studies have established that the crosslinked polymer nanostructures can help the development of novel devices for various medical and industrial applications (Baek et al. 2018). The nanocomposite crosslinked polymers are robust and have a greater capacity for controlled drug release (Pellá et al. 2018). This polymer structure allows a better quality of life by intra-peritoneal administration of the chemotherapy drug for the cancer patient (Jamal et al. 2018). According to Fisher et al. (2018), hyaluronic acid (HA)-based crosslinked polymers have been studied for their effect on the invasion of breast cancer cells, and the results have shown that upon increasing the crosslink density, the invasion of cancer cells from breast decreases. This study proves that the crosslinked polymers could be a promising candidate in cancer treatments (Huang and Huang 2018).

4.4.4 Contact Lenses and Ocular Implants

The production of contact lenses is one of the most widely used applications of crosslinked polymers, while one of the main properties of the crosslinked polymers is their ability to be perfectly tailored to the global ocular curvature (Schafer et al. 2018). In addition, they allow the oxygen to permeate the cornea by diffusing into the lens. One of the methods used in the contact lens production industry is the Lathe cutting technique, in which the lenses would be molded from ‘buttons’ of solid dehydrated crosslinked polymers (Fig. 4.2) (Caló and Khutoryanskiy 2015). According to Maulvi et al. (2016), the crosslinked poly(2-hydroxyethyl methacrylate) (PHEMA) polymers have been used for producing contact lenses, due to their mechanical properties and biocompatibility. In addition, a significant number of companies have developed a range of crosslinked polymer contact lenses compounds comprising different types of monomers in order to acquire a contact lens that holds the highest amount of water content and mechanical properties, thus allowing the lens to resist the eyelid strength with an increased oxygen permeation (Pitt et al. 2015). Furthermore, with these applicable contact lenses, this has increased the researches in the field of ophthalmic drug delivery, due to their ability to increase the residence time of the drug in the precorneal region that is provided due to the geometric barrier of the lenses to the medicine upon the diffusion out of the gel matrix to the tear film (Wolffsohn et al. 2015).

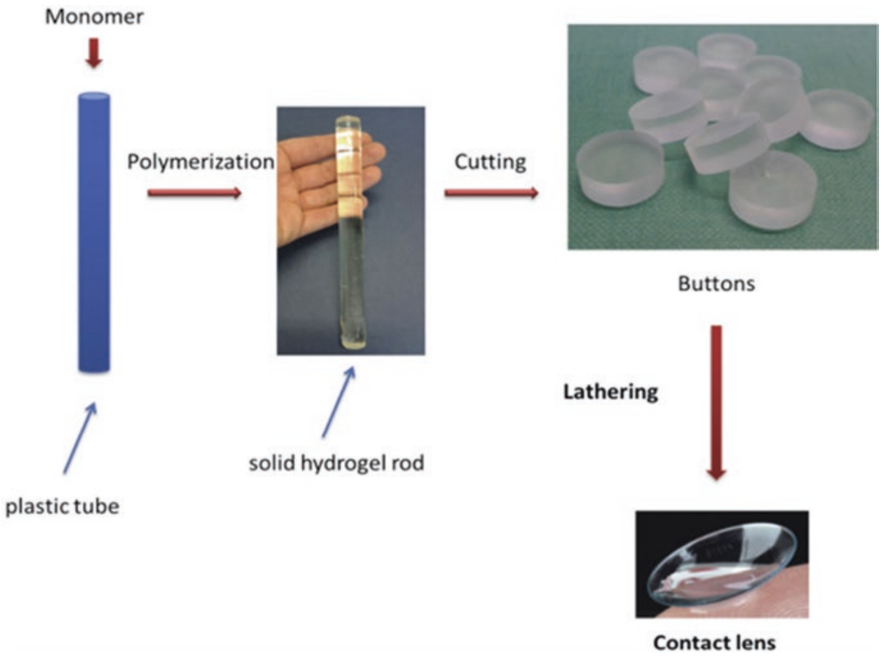

Fig. 4.2 Schematic representation of Lathe cutting technique for the production of contact lenses. Adapted with permission from Caló and Khutoryanskiy (2015)

4.4.5 Drug Delivery

Crosslinked polymers right after their discovery were used in antibiotics and anti-cancer drug delivery researches (Deen and Loh 2018). They have been seen as a potential solution to achieve a sustainable and targetable drug release at appropriate and specific sites, while working on increase the influence of the drug and decrease its side effects simultaneously (Xing et al. 2015). Crosslinked polymers have a porous system, which could eventually be controlled by the compactness of the crosslink or by altering the swelling affinity of the polymer in the environment (Sharma et al. 2018). Due to this porous property, this aids the crosslinked polymer gels release the drugs, which is achieved by monitoring the diffusion coefficient of the drugs (Fig. 4.3) (Wang et al. 2016). Crosslinked polymers when used through topical transdermal application, comprise many advantages, since they prevent liver metabolism, and therefore, increase the drug effectiveness and bioavailability (Culver et al. 2017). Due to the swelling property of the crosslinked polymers, they promise to be used in transdermal drug delivery, since the crosslinked polymer are similar to living tissues which can be effortlessly removed compared to ointments or patches (Dimatteo et al. 2018). In addition, crosslinked polymers comprising gentamycin have been shown to be more efficient in the treatment of skin infections compared to parenteral delivery of the gentamycin which causes severe disorders (García-Astrain and Avérous 2018).

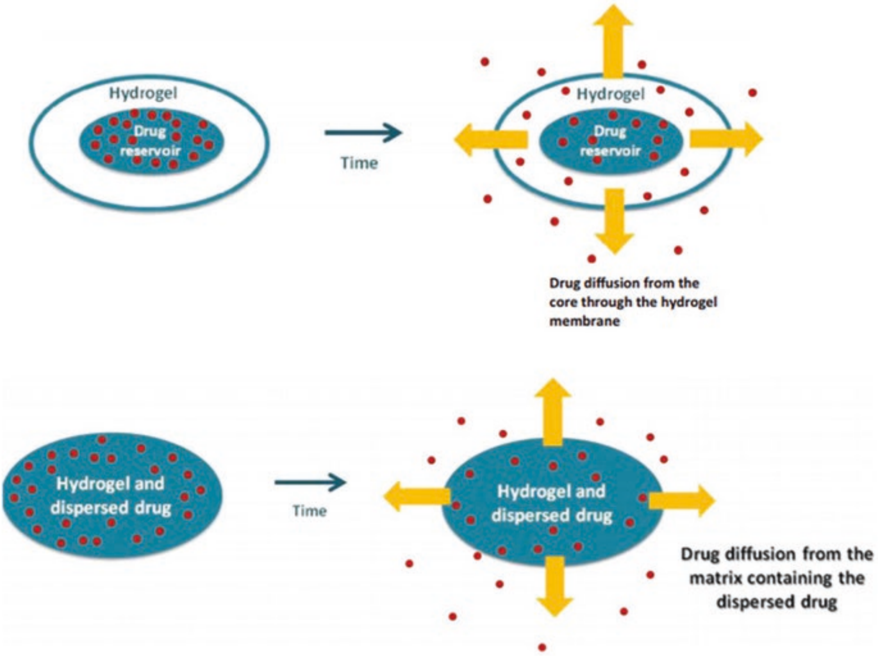

Fig. 4.3 Schematic representation of the release of a drug through a crosslinked polymeric membrane and a matrix. Adapted with permission from Li and Mooney (2016)

4.4.6 Gene Delivery

Crosslinked polymers have been proposed as a promising candidate for gene delivery, since they can reserve the activity of the viral and non-viral vectors, and protect them from the immune system attack (Yang et al. 2016). Crosslinked hydrogels can be injectable, in addition to being biologically sensitive, so it has great promise in the field of gene delivery (Nurunnabi et al. 2015). On the other hand, the crosslinked polymers implemented in the gene delivery require advanced strength for the prolonged transgene expression to occur (Nguyen et al. 2017). According to Zhang et al. (2017), lentivirus gene therapy is generated from crosslinked fibrin polymers comprising hydroxyapatite NPs that have the ability to interact with the lentivirus and the fibrin, this interaction leads to the stabilization of the crosslinked polymer and subsequently improved the vector release and cell infiltration rate. Therefore, with the appropriate biomaterial system and vector, gene delivery could be improved, thus improving transgenic expression (Xiang et al. 2017).

4.4.7 Oil Sorbers

Crosslinking with chemical covalent bonds linking the crystalline and amorphous domains is responsible for the 3D network structure that characterizes these materials. This drastically improves a large number of low-, room- and especially high temperature properties, such as abrasion, chemical and stress- cracking resistance impact, heat deformation, tensile strength and viscous deformation, and also adds new useful properties, such as shape memory. The elasticity and swelling properties are attributed to the presence of chemical or physical crosslinks within the polymer chains. Many authors have reviewed the advances in crosslinking technology for oil sobers. For example, Jang and Kim (2000) studied the copolymerization of styrene monomer with several long-chain alkyl acrylate monomers such as, 2-ethylhexyl acrylate (EHA), lauryl acrylate (LA), lauryl methacrylate (LMA) and stearyl acrylate (SA). These acrylates with long chain alkyl groups are generally known as hydrophobic materials. Therefore, a highly absorbent property of oil can be obtained by controlling the composition and the crosslinking density of the copolymer.

Jang and Kim (2000) conducted a detailed study on the swelling properties of the crosslinked copolymers. The influence of the synthetic variables (amount of crosslinking agent and initiator, monomer feed ratio, polymerization temperature and type of acrylate monomer) of the crosslinked copolymers on the oil absorption capacity was examined.

Atta and Arndt (2005) synthesized new oil- absorbing polymers containing alkyl acrylate *via* different types of chemical crosslinkers and irradiation techniques. These authors conducted a detailed study on the swelling properties of the crosslinked 1-octene-isodecyl acrylate copolymers. The crosslinking polymerizations were carried out in the presence of different concentrations of ethylene glycol diacrylate (EGDA) and ethylene glycol dimethacrylate (EGDMA) crosslinkers *via* catalytic initiation and electron beam irradiation at a dose rate of 80 kGy. More oil sorption capacities were performed upon using longer alkyl acrylate, reaching a maximum of 20.5 and 38.8 g of crude oil/g of sample, respectively. In addition, crosslinked reactive macromonomers based on octadecyl acrylate (ODA) and polyisobutylene modified with maleic anhydride and cinnamoyloxy ethyl methacrylate (CEMA) moieties were prepared and oil sorption was evaluated. Farag et al. (2011) also synthesized linear and crosslinked copolymers with different compositions of 1-hexadecene and trimethylolpropane distearate monoacrylate monomers, and evaluated the oil absorption. Different concentrations of EGDA and EGDMA crosslinkers were varied from 0.5 to 2%. These authors concluded that the oil absorbency and swelling rate were mainly influenced by the DC and the hydrophobicity of the copolymer units. Keeping this in view, El-Ghazawy and Farag (2014) prepared a series of comb-like crosslinked dodecyl acrylate-*co*-ODA-*co*-vinyl acetate terpolymers (DOVs) with four different feed ratios of vinyl acetate while remaining constant the other monomer ratios. Crosslinking was carried out using trimethylol propane triacrylate (hexafunctional) or divinyl benzene (tetrafunctional). The structure-performance relationship was discussed, especially with respect to crosslinker type, crystallinity and feed ratio. These authors found that the highest oil absorption of crosslinked DOVs was 43.22 g of oil/g of sample after 20 min. of immersion. Lauren et al. (2014) illustrated an example system of thermally crosslinked octene-styrene-divinylbenzene (OS-DVB) copolymers. In the molecular models, the DC was ranged from 0 to 100%, and the resulting structural and thermal properties were examined. The simulations reveal an increase in the free volume with higher DCs.

On the other hand, Abdel-Azim et al. (2007) synthesized porous crosslinked copolymers for the sorption of oil spills by CEMA copolymerized with different monomer feed ratios of ODA and crosslinked using AIBN as a initiator and *N*,*N*′,*N*″-trisacryloyl melanine (AM) or *N*,*N*′,*N*″-trismethacryloylmelanine (MM) as crosslinkers. These authors observed that the sol fraction values of the CEMA/ODA crosslinked copolymer were lower when MM was used instead of AM, and the thermal stability of the crosslinked network increased as the ODA concentration increased and also in the presence of MM crosslinker, as a consequence of a higher crosslinking density. In addition, SEM results showed micropores that were formed as the ODA content increased. Similarly, the flexibility of the network was improved by incorporating MM instead of AM.

El-Ghazawy et al. (2014) prepared linear and branched polyesters by transesterification of methyl recinoleate without or with diethylene glycol, pentaerithirtol or trimethylol propane for different durations. Mws of the synthesized polyesters were determined using gel permeation chromatography and hydroxyl number. As an example, Fig. 4.4 represents the crude oil sorption by the crosslinked polymethyl recinoleates.

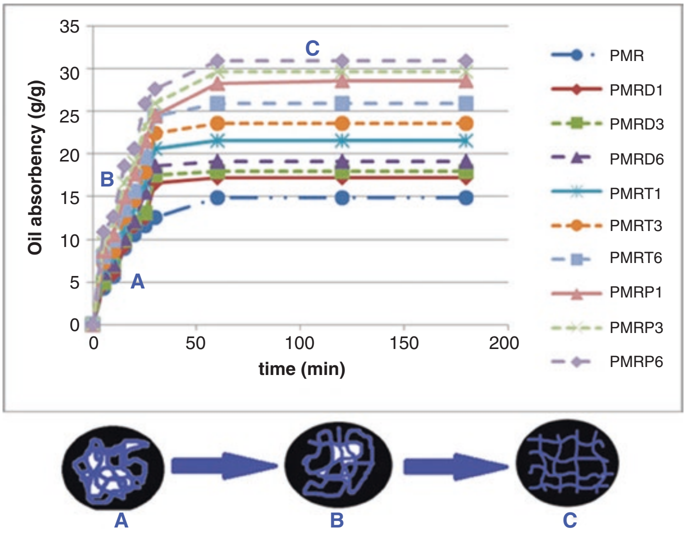

Fig. 4.4 Crude oil sorption by crosslinked polymethyl recinoleates. Reproduced with permission from El-Ghazawy et al. (2014)

4.4.8 Plastic Replacement

Plastics are synthetic polymers, which are considered easy to manufacture, as well as being economical and efficient, although they are not ecological. Previously, crosslinked gels were not perceived as suitable alternatives to plastics (Kondo et al. 2015). However, it was discovered that when the crosslinked polymer is binds to clays, they retain properties as robust and can be easily molded, in addition to having the ability to self-heal when cut, thus allowing them to be a potential substitute for plastics (Cuadri et al. 2018).

4.4.9 Prevention of Soil Erosion

Crosslinked polymers have been applicable in the field of the environment for more than a decade, while the soluble crosslinked polymers have been used to reduce the soil erosion and improve the water infiltration from fine agricultural soils (Hotta et al. 2016). According to Guilherme et al. (2015), the soluble crosslinked PAAm polymers are dissolved in the irrigation water to form a thin slimy film that would protect the soil surface of the wash floor. As the irrigation water causes erosion to bare soils, and by the presence of a thin film that could hydrate the soil and allow irrigation water to permeate easily (Cheng et al. 2018). Several investigations have been carried out on different types of soils using the crosslinked PAAm polymer, which are suitable for soil degradation and erosion (Kabir et al. 2017). It has also been shown that the use of anionic soluble crosslinked PAAm polymer is more efficient than cationic crosslinked PAAm polymers in reducing soil erosion (Neethu et al. 2018).

4.4.10 Wound Dressing

The treatment that is applicable for damaged skin and the diabetic ulcers. These polymers are used prosthetic skin engineering and have a high value, since it implies many requirements for patients that are generally not met (Hamedi et al. 2018). Thus, wound dressing is considered the potential new way to restore damaged skin tissues and diabetic ulcers with the applicability of high biocompatible bioactive compounds (Mohamad et al. 2018). Crosslinked polymers can retain the water and the injected drug for an enough time. Attributing to this ability, they were applied to contain wound exudates (Qu et al. 2018). According to Kamoun et al. (2017), the sodium alginate and the gelatin crosslinked polymers have been used to protect and cover the wounds from any bacterial infections. Zhang et al. (2015a, b) found that gelatin and HA crosslinked polymers are promising compounds for the treatment of skin regeneration.

4.5 Conclusions

This chapter gave a general description of the crosslinked polymer hydrogels, forms of the polymers (biological, chemical and physical), processes and methods for preparation (free-radical polymerization, condensation polymerization, bulk polymerization and ultra-violet radiation). In addition, the chapter shows the swelling, mechanical and biocompatible properties of crosslinked polymers. An emphasis on different applications of hydrophilic networks mentioned in literature is provided. Finally, the chapter shows several workers have successfully use oil sorbers with their different categories in cleaning oil spills for hydrophobic networks applications.

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Conflicts of Interest The authors declare no conflict of interest.

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