

Chapter 5

Polysaccharide-Based Polymer Gels



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Abstract Hydrogels are special polymer systems with unique properties due to their high water content. They hold a relative large importance in several application fields, especially in the medicine and sanitary products. Moreover, their potential utility is intensively studied in several other fields. While most commercially available hydrogels are synthetic polymer-based, there is an increasing interest in the use of various renewable resources. Such materials have several advantageous properties, like biodegradability and good biocompatibility. Polysaccharides are the most important group of the renewable materials due to their abundance and low cost. In the present chapter, we give an account of the potential use of polysaccharide systems for the formation of hydrogels. After a short introduction to the chemical structure of polysaccharides, their dissolution, possible crosslinking methods, and the studies related to the most important representatives are discussed. The modification of gel properties by grafting, copolymerization, and blending is also a very common route. The non-polysaccharide component can range from other renewable resources like polypeptides to synthetic polymers to inorganic additives. Finally, we give a summary of the potential applications of the polysaccharide-based hydrogels.

Keywords Polysaccharide · Hydrogel · Superabsorbent · Crosslinking

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1 Introduction

Gels are special three-dimensional polymer networks where the polymer matrix is filled with liquid or gas. The polymer network can be physically or chemically crosslinked. In case of physical gels, the network formation occurs due to various weak interactions, like the entanglement of the polymer chains, hydrogen bonds, or van der Waals interactions. Such structures are usually not permanent and they dissolve over the time when immersed in their solvents. However, the polymer chains can also be crosslinked through chemical reactions, leading to strong covalent bonds. The chemically crosslinked network is much more stable and cannot be dissolved without the degradation of the polymer. Therefore, chemical gels are usually preferable in the majority of the application fields.

Hydrogels are special gels filled with water or are capable of absorbing large amounts of it. The swelling behavior heavily depends on the chemical structure of the polymer: for high water uptake, the presence of hydrophilic groups in the polymer backbone is favored. Moreover, other effects like the electrostatic repulsion between charged groups also contribute to the network expansion, leading to improved swelling. Hydrogels with an exceedingly high water absorbing capacity (usually hundreds or even thousands times of their own weight) are called super-absorbents. The high water content has a major impact on the gel behavior: such gels are very soft and special properties like biocompatibility are also easier to develop. Moreover, depending on the chemical structure, hydrogels can also exhibit responsive behavior to the environmental conditions, such as the pH or the temperature. This sensitivity can be very advantageous and allows new possible applications.

Nowadays hydrogels already have a wide array of commercial applications due to the intensive research thanks to their unique properties. They are especially widespread in the medicine and pharmacy, where they are used mainly in drug delivery, tissue engineering, and wound dressing. Their use is widespread in hygienic products like diapers, as well. Moreover, there are a large number of studies focusing on the application in new fields such as the agriculture and wastewater treatment. Most commercially available hydrogels are synthetic polymer-based. The use of acrylates (various salts and esters of acrylic acid) holds an especially important place in the hydrogel production and application. Such gels exhibit excellent swelling properties, non-toxicity, and responsive behavior. However, in certain fields their potential use is limited. For example, their agricultural application is hindered by their poor biodegradability.

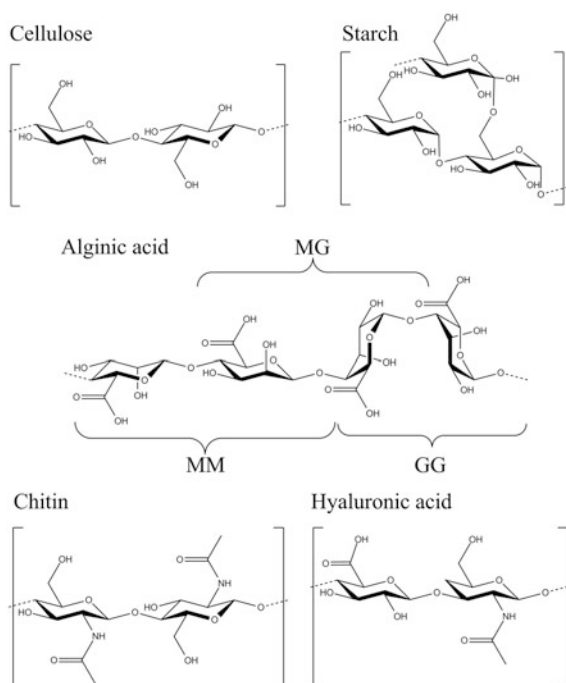
There is also a growing interest in the replacement of synthetic polymers with different renewable resources. Such materials are not only cheap and available in abundance but also more environmentally friendly. A very important aspect is the lack of toxicity: unlike their polymers, the acrylate monomers are toxic; thus, their residues need to be carefully removed after the synthesis. Hydrogels based on natural polymers show excellent biodegradability, which is a possible requirement depending on the application. The most important renewable materials are the

polysaccharides. The major focus is on the most abundant polysaccharides, such as the cellulose, chitin, starch, and alginate. These polymers are not only used in their native form, but the utilization of their derivatives is also significant. The modification is relatively easy and cheap due to the reactive hydroxyl or other pendant groups. A very important aspect that led to the investigation of their derivatives is the dissolution: depending on the chemical structure and molecular properties, water solubility can be easily achieved for the derivatives of polymers normally insoluble in water; thus, no special solvents are required. Moreover, the substituents introduced with the functionalization also lead to new gel properties.

2 Chemical Structure of Polysaccharides

The chemical structure of the various polysaccharides holds a lot of similarities (Trache et al. 2017; Corobea et al. 2016; Voicu et al. 2016; Miculescu et al. 2016). The most common structural unit is the glucose and its derivatives, but other saccharides also common components in certain polymers (Fig. 1). Due to the differences in the structural units and in the supramolecular structures, their properties are very different; thus, the crosslinking strategies differ significantly. Therefore, a short overview is given for the most common polysaccharides used for hydrogels.

Fig. 1 Chemical structure of the most common polysaccharides



2.1 Cellulose and Its Derivatization

Cellulose is the most abundant material in the world. It is present mostly in plant cells, but it is synthesized by some bacteria, as well. It consists of β -D-glucose units which form a linear chain with $\beta(1 \rightarrow 4)$ linkages. The presence of hydroxyl groups leads to the formation of intermolecular and intramolecular hydrogen bonds, while apolar parts of the macromolecules are linked with van der Waals interactions (Gross and Chu 2010). The cellulose chains form a semicrystalline structure consisting of crystalline and amorphous regions. Moreover, in the latter region, semi-ordered structures are also present to a certain degree. The polysaccharide has multiple crystalline polymorphs: Cellulose I, II, III, and IV. In the nature, Cellulose I is the dominant structure, which consists of parallel polymer chains and is formed by two different phases: the monoclinic I_α and the triclinic I_β . While both phases are present simultaneously, in higher plants the I_β , in bacteria and algae the I_α phase are the dominant (Sugiyama et al. 1991). The other cellulose polymorphs are usually synthesized by the conversion of Cellulose I, but the natural formation of the thermodynamically more stable Cellulose II was also observed (Hirai et al. 2002).

Due to the strong intermolecular interactions, the cellulose is insoluble in water. However, the partial substitution of hydroxyl groups results in the weakening of these bonds, leading to improved solubility. The water solubility increases with the degree of substitution which leads to weaker polymer–polymer interactions. For the hydrogel synthesis, mostly the cellulose ethers are utilized; the importance of its esters is minimal in this field. Cellulose ethers are important industrial materials with a wide array of applications such as surfactants, coatings, and thickeners. During the derivatization, the cellulose is disintegrated first in concentrated alkali followed by the substitution reaction (the alkaline environment also functions as a catalyst) (Woodings 2001). Carboxymethylcellulose is prepared with the addition of chloroacetic acid, leading to the formation of the sodium salt of the derivative. For the synthesis of alkylcelluloses alkyl chloride, in case of hydroxyalkylcelluloses alkene oxide is used as a reagent. Alkylhydroxyalkylcelluloses are also common derivatives, where both types of pendant groups are present in the structure.

2.2 Starch

Starch is another major polysaccharide which consists of α -D-glucose units. It is mostly present in plant cells as granules for energy storage. The glucose units form two different macromolecular structures: amylose and amylopectin. The amylose is a linear macromolecule where the glucose units are linked with $\alpha(1 \rightarrow 4)$ bonds. Amylopectin has a similar structure but it also has branches due to the $\alpha(1 \rightarrow 6)$ linkages. There is also a major difference in the molecular weight as the linear amylose is a significantly smaller macromolecule. The chains organized in double

helices which form the crystalline structure. Starch has two allomorphs: type A and type B starch (Buléon et al. 1998). Both structures consist of ordered double helices, but their position differs significantly. In A-type starch, the helices are closely packed, and the water molecules are positioned between the helices. For B-type starch, the helices form a hexagonal lattice, where the water is inside the hexagonal structure. C-type starch consisting of the mixture of the A and B-type structures also exists, though related studies are limited (Bogacheva et al. 1998). The oriented helices form the crystal lamellae, while the branch points are part of the amorphous phase, leading to a semicrystalline structure. Starch is present in the plant cells in granule form, which consists of alternating amorphous and crystalline regions; lipids and proteins are also present on its surface. Moreover, other components like phosphates and phospholipids are also found in the granule depending on the source. As the granular structure is not destroyed before the starch is used for the hydrogel synthesis, it has a major effect on the mechanism of the gelation.

While there is a large interest in the derivatization of the starch (Gotlieb and Capelle 2005), currently only the carboxymethylation (prepared with chloroacetic acid in sodium hydroxide solution similarly to the other polysaccharides) is relevant for the gel synthesis.

2.3 Chitin and Its Derivatization

Chitin is the most abundant material after the cellulose. It is a very important structural unit in the nature, especially for the fungi in the cell walls and as the exoskeleton for a wide array of animals. The chemical structure of chitin is similar to the structure of cellulose. It consists of β -D-glucose groups linked by $\beta(1 \rightarrow 4)$ linkages, but the hydroxyl groups in the C(2) position are substituted by an acetamido group; thus, *N*-acetyl- β -D-glucosamine is the structural unit. There are strong intermolecular interactions between the chitin chains due to the hydrogen bonds between the NH and CO groups, leading to a strong crystalline structure and insolubility in water. Chitin forms three different crystalline polymorphs: α -chitin consists of antiparallel chains, and β -chitin is formed by parallel macromolecules, while the γ polymorph has a more unique structure as two parallel chains are followed by an antiparallel one (Hudson and Smith 1998). Unlike the cellulose, all three polymorphs are present in the nature.

Chitin derivatization is usually achieved through modification of the acetamido groups. The most important derivative is the chitosan which is prepared by the deacetylation of chitin, leading to amino groups in the C(2) position. While full deacetylation is possible (Domard and Rinaudo 1983), the process is usually incomplete; thus, *N*-acetyl- β -D-glucosamine units are still present in the polymer structure. Unlike the chitin, chitosan is soluble in aqueous solutions at acidic pH due to the protonation of the amine groups (Rinaudo et al. 1999).

The hydroxyl groups in the polymer chain can also be utilized for the functionalization. For example, by introducing carboxymethyl groups, a fully

water-soluble chitin and chitosan derivative can be prepared (Muzzarelli 1988). However, these derivatives hold much smaller importance than the chitosan.

2.4 Alginate

Alginates are the salts of the alginic acid, from which the sodium salt is present in abundance in the nature. Alginate is synthesized by various algae and bacteria; for the industrial use, usually brown algae is used as alginate source. Unlike alginic acid, the alginate is water soluble. It is a linear copolymer of two monomers: β -D-mannuronic acid (M) and α -L-guluronic acid (G), with (1 \rightarrow 4) linkages between the units. These bonds can also form between the same units, leading to the formation of homopolymer (GG and MM) and copolymer blocks (MG) with different properties in an alternating structure (Donati and Paoletti 2009). The properties of the alginate heavily depend on the ratio of the two monomers and the distribution of the blocks (Johnson et al. 1997).

2.5 Hyaluronic Acid

Hyaluronan or hyaluronic acid is a unique polysaccharide due to its versatility. It is naturally present throughout the body of mammals in its salt form. The repeating unit consists of D-glucuronic acid and N-acetyl-D-glucosamine units with β (1 \rightarrow 3) linkage. These disaccharide units are linked with β (1 \rightarrow 4) bonds, forming a linear macromolecule of very large molecular weight (Fraser et al. 1997). While it is not as easily available as other abundant polysaccharides, there is a major interest in it due to its favorable properties for medical applications.

3 Dissolution of Polysaccharides

While gels can be synthesized from both solution and in dry state, the latter method is very rarely used for polysaccharide-based systems; thus, the dissolution of the polysaccharide is a key factor in the gel preparation. Unlike low molecular weight molecules, the dissolution of macromolecules is much more difficult. The solubility depends on the polymer–solvent and polymer–polymer interaction: if the latter one is dominant, the solvent cannot disrupt the intermolecular bonds between the macromolecules. Thus, the solvent properties are decisive. The most important solvent is the water due to its advantages. A wide array of polysaccharides like alginate and hyaluronic acid are water soluble. Therefore, water is the standard solvent for these polymers unless other water-insoluble components are also added. However, the most abundant polysaccharides (cellulose, starch, and chitin) are not

soluble in water; thus, special solvents are required. While a wide array of solvents are available for the dissolution of these polymers, in the following section, only solvents utilized for the hydrogel synthesis are reviewed.

3.1 Dissolution of Cellulose and Its Derivatives

The dissolution of cellulose was extensively studied in the past decades. There were major efforts to find cost-effective, environmentally friendly solvents. For the hydrogel synthesis, usually its industrial solvents are used, but there is strong interest toward novel systems like ionic liquids, as well. However, not all common solvents were investigated for this application so far. For example, dimethyl sulfoxide (DMSO)-based solvent systems are mostly used only for the synthesis of aerogels (Innerlohinger et al. 2006). Similarly, *N*-methylmorpholine-*N*-oxide, the solvent used for manufacturing regenerated cellulose fibers (e.g., Lyocel, Tencel), currently holds little importance in the gel preparation, but it might gain more attention in the future. Several solvents, such as cupriethylenediamine (CUEN) hydroxide, depend on the formation of metal–ion complexes with cellulose. CUEN and its relatives with different metals and ammonium hydroxide find substantial industrial use (Johnson 1985). Cuprammonium hydroxide (a mixture of copper hydroxide and ammonium hydroxide) and phosphorous acid had been used for regenerated cellulose fiber production for a long time (Kotek 2007); they might attract the interest of the cellulosic gel producers in the future.

For the hydrogel synthesis, multiple solvents of cellulose are widely used. The dimethylacetamide/lithium chloride (DMAc/LiCl) system is one of the most common such solvents. The mechanism of the process was in-depth investigated: the hydrogen bonds between the cellulose chains break up due to the chloride ions forming hydrogen bonds with the hydroxyl groups (Striegel 1997). Solvent exchange further improves the dissolution: the cellulose is immersed in water, which is gradually exchanged to methanol, and finally to DMAc/LiCl (McCormick et al. 1985). Such systems are not only stable, but the dissolution occurs without degradation even for high molecular weight cellulose at low temperatures (Dupont 2003). However, Potthast et al. (2002b) observed that elevated temperatures (over 85 °C) lead to the rapid degradation of the polymer.

Another method to dissolve cellulose is the addition of urea or thiourea to alkali hydroxide aqueous solutions. Sodium hydroxide is a cheap solvent of cellulose, but it is suitable only for the dissolution of low molecular weight polymer (Isogai and Atalla 1998). However, the introduction of urea or thiourea leads to the significantly improved solubility of the polysaccharide. The process is explained by the stabilizing effect of the components: Na⁺ cations interact with the hydrophilic groups of the cellulose (Cai and Zhang 2005), while the urea stabilizes the hydrophobic parts, preventing the intermolecular interactions between the polymer chains (Xiong et al. 2014). Due to this dual effect, the ratio of the two components is important: both too high hydroxide and too high urea content lead to decline in the solubility (Zhang et al. 2010).

Recently, the use of ionic liquids as novel solvents is also showing a growing tendency. Ionic liquids are organic salts with melting point below 100 °C, commonly even below the room temperature. Unlike the aforementioned solvents, they offer a more environmentally friendly option due to the low toxicity and biodegradability. However, this is not universally true for all salts: depending on the chemical structure, some ionic liquids not only show poor biodegradability but also are more hazardous than conventional solvents (Gatherhood et al. 2004; Romero et al. 2008). The chemical structure of the salt also plays a major role in the process: it not only affects the dissolution but some salts can also react with the cellulose (Clough et al. 2015). The latter process may lead to undesirable changes in the polymer properties; thus, it should be avoided. Swatłowski et al. (2002) investigated the dissolution of cellulose in different alkyl-methylimidazolium systems and noted that the alkyl chain and the anion have a major effect on the solubility. While a wide array of methylimidazolium-based ionic liquids proved to be an efficient solvent (Feng and Chen 2008), most commonly 1-allyl-3-methylimidazolium chloride (AMIMCl) is used for the hydrogel synthesis (Zhang et al. 2005b). These salts are not only capable of dissolving large amounts of cellulose, but the polymer degradation is observed only at high temperatures. While they also have some disadvantages like the high viscosity or the slow dissolution, its widespread use is mainly hindered by the high production costs compared to the classic solvents.

Another method to achieve water solubility is the partial substitution of the hydroxyl groups, which weakens the strong intermolecular interactions, thus improving water–polymer interactions. Water solubility heavily depends on the molecular mass, degree of substitution (D_S), and substituent, as well. For example, a minimum D_S of 0.4 is required for carboxymethylcellulose to be fully water soluble (Wertz et al. 2010). In case of nonpolar substituents like methyl groups, an even higher degree of substitution is needed for optimal solubility. Moreover, heterogeneous distribution also leads to a decrease in the solubility, as the intermolecular bonds are not disrupted in certain segments of the chains. The derivatization is especially important for the cellulose, for which a wide array of substituents groups are used. The most common derivatives are the carboxyalkyl, alkyl, hydroxyalkyl, and alkylhydroxyalkylcelluloses.

3.2 *Dissolution of Starch and Its Derivatives*

Similarly to the cellulose, native starch does not dissolve in water due to the strong polymer–polymer interactions. Amylose and amylopectin, the two components of starch form a semicrystalline granule structure. These granules are resistant to external effects and while they show some swelling in water, they are insoluble. However, increasing the temperature of the aqueous dispersion leads to gelatinization: the interactions between the polymer chains are weakened, the ordered structure is disrupted, and the swelling of the granules increases significantly (Miles et al. 1985; Hoover 2001). The high viscosity of the gelatinized starch allows the

homogeneous dispersion of the crosslinking agents and other monomers in the system. This method is widely used for the preparation of copolymer gels as water is sufficient instead of more expensive and less “green” solvents.

Derivatization is also a possible way to achieve water solubility. However, opposed to the cellulose, for starch the derivatization is much less significant as the more convenient gelatinization is preferred. Moreover, only the gelation of its carboxymethyl derivative was investigated so far in this field (Nagasawa et al. 2004).

3.3 *Dissolution of Chitin and Chitosan*

Chitin is highly crystalline as the acetamide groups also participate in the formation of the intermolecular bonds. Solvents similar to the ones utilized for the cellulose dissolution are used to disrupt the intermolecular interactions. For example, sodium hydroxide/urea system proved to be excellent solvents for the chitin (Hu et al. 2007). Low temperature promotes the destruction of the intermolecular bonds as the polymer–solvent interactions become more stable (Chang et al. 2011a). Another popular solvent is the so-called Ca solvent, which is CaCl_2 dihydrate dissolved in methanol. The water present in the CaCl_2 also plays a major role in the mechanism as Ca solvent prepared from anhydrous chloride salt does not dissolve the chitin (Tamura et al. 2006). Tetrabutylammonium fluoride/dimethyl sulfoxide and lithium chloride systems were also applied successfully; for the latter system, *N*-methyl-2-pyrrolidone was used for the dissolution of the salt (Yoshimura et al. 2005). Recently, the application of ionic liquids was also studied and the imidazolium salts proved to be very efficient.

Chitosan, the deacetylated derivative of chitin is an even more popular choice for the hydrogel preparation. While pure water is an inadequate solvent, aqueous solution of chitosan can be prepared in presence of acidic medium like acetic acid; thus, the gel synthesis is easier compared to chitin. However, chitosan is also often derivatized further to modify the gel properties: the swelling properties of the hydrogels significantly improve at nonacidic pH if carboxymethyl groups are introduced to the polymer (Vaghani et al. 2012). Thus, the carboxymethylchitosan is also a major subject of such experiments. Moreover, carboxymethylation is also a viable route to increase the water solubility of the chitin polymer; thus, deacetylation is not required to allow the use of aqueous solutions for the gelation (Zhao et al. 2001).

4 **Crosslinking Methods**

The dissolution of the polysaccharide is followed by the crosslinking the polymer chains to form the three-dimensional network. In solutions, the polymer chains are highly mobile; thus, the crosslink formation is easier. A wide variety of methods are

employed for the synthesis of hydrogels. The properties of the polysaccharide are the determining factor which crosslinking steps are applicable; thus, the preferred method is polymer-dependent. For the physical crosslinking, three major strategies are available: gelation induced by high temperature, solvent exchange, or complexation through ionic interactions. On the other hand, chemical crosslinks are reached by adding crosslinking agents or initiating the formation of reactive free radicals. The latter method can be initiated either by chemical initiators or by high-energy irradiation. In the following, a short general summary is given for these methods.

4.1 Physical Gelation

4.1.1 Thermal Gelation

Temperature-induced gelling is a classic method for the preparation of physical hydrogels. In aqueous solution, the polymer chains are surrounded by the water molecules which weaken the polymer–polymer interaction. However, increasing the temperature leads to the gradual dehydration of the chains; thus, the macromolecules can interact again with each other, leading to the aggregation of the polymer chains. This method is very commonly used for polymers containing various hydrophobic groups like alkyl chains due to the increasing hydrophobic interactions at elevated temperatures (Sarkar 1979). The thermal gelation is usually thermoreversible: the physical network gradually falls apart at low temperatures due to the hydration. However, for some polymers like native cellulose the process are irreversible; thus, the cooling has no effect on the gel structure (Cai and Zhang 2006).

The low temperatures also help the strong interaction between the polymer chains. In the freeze-thawing method, the solution is stored in frozen state and then thawed in multiple freezing cycles (Yang et al. 2008). In the frozen solution, multiple phases are present: the frozen solvent, the polymer-rich phase, and the transition between them. The high polymer concentration leads to strong interaction between the chains, aiding the interactions. Moreover, the polymer-rich region is not frozen due to the significantly lower freezing point. The chain mobility in moderately frozen state not only allows the formation of physical networks, but it can even be utilized for chemical crosslinking at low temperatures (Yang et al. 2008).

4.1.2 Coagulation by Solvent Exchange

An interesting method to prepare physical gels is the solvent exchange. After the dissolution a non-solvent is added to the solution—as the ratio of the good solvent decreases, the interaction between the macromolecules increases, ultimately leading

to aggregation and formation of the physical gel. To utilize this method for the hydrogel formation, the polymer must be insoluble in water so they do not dissolve in the aqueous environment. This strategy is mostly used for the cellulose-based gels, where the cellulose is dissolved in various solvents and then water is added to promote the gel formation (Potthast et al. 2002a; Kadokawa et al. 2008; Östlund et al. 2009). However, gelation of the whole system occurs only over a critical polymer concentration: in very dilute solutions only the aggregation and precipitation of the polymer was observed (Ishii et al. 2006). In LiCl/DMAc solutions the ionic strength is also a determining factor in the dissolution of cellulose. Therefore, the deionization of the system also leads to reduced solubility and gelation. The precipitation method is also used in the manufacturing of some regenerated cellulose fibers: after dissolution of cellulose in NMMO/water system, the precipitation is carried out by stepwise addition of water (Loubinox and Chaunis 1987). As this technology shows, the change of the solvent system properties to promote the aggregation does not necessarily need the introduction of another solvent.

4.1.3 Complexation (Ionic Crosslinking)

The ionic interactions can also be exploited for the formation of physical crosslinks. Several polysaccharides have charged pendant groups on the polymer chains, most commonly carboxylic groups. These groups can interact with their counterions and weak ionic bonds are formed between them. However, if multivalent counterions or polymers with oppositely charged groups are present, they can interact with multiple charged pendant groups and form intramolecular and intermolecular bonds (George and Abraham 2006). This method allows a relatively easy gel formation, though the physical network is relatively weak. The ion complexation is the most important gelation method for the alginates, including the industrial production. Alginate gels are formed with the addition of calcium ions through the interaction with the carboxyl groups, leading to a special egg-box structure (Grant et al. 1973). However, not only other divalent cations proved to be efficient crosslinkers (Yang et al. 2013) but also the ion complexes formed with trivalent cations like Al^{3+} led to an even stronger network structure (Rochefort et al. 1986). Moreover, valence is not the singular determining factor as ions with the same valence show different efficiency in the gel formation (Menakbi et al. 2016).

4.2 Chemical Gelation

4.2.1 Chemical Crosslinking with Crosslinking Agents

The most common method for chemical crosslinking is the use of crosslinking agents. These reagents contain groups which can easily react with the pendant functional groups on the polymer backbone. To form crosslinks, the crosslinking

agents need to be at least bifunctional so they can react with at least two pendant groups on different chains. For polysaccharides, usually a large number of reactive hydroxyl groups are present on the polymer backbone; therefore, crosslinkers which easily react with these groups have the largest importance. Reactions involving other common pendant groups like carboxyl groups are also common, but their utility is more limited.

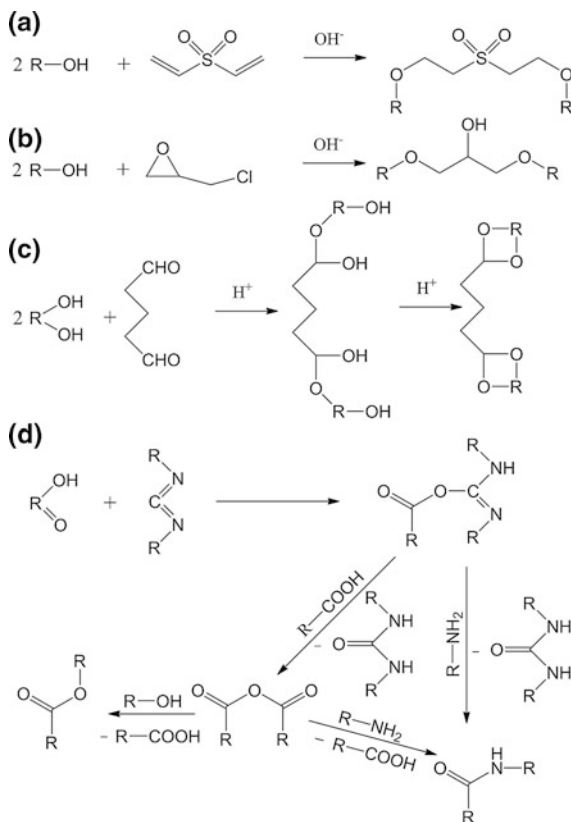
One of the major crosslinking agents is the divinyl sulfone (DVS). The crosslink formation occurs through the reaction of the vinyl and hydroxyl groups (Fig. 2a). However, this requires alkaline pH because the hydroxyl groups are needed to be deprotonated. Therefore, dilute aqueous solutions of potassium hydroxide are used as solvents instead of water to promote the crosslinking (Esposito et al. 1996). The major drawback of the DVS is the high toxicity: while it does not have a harmful effect on the environment after the reaction, the unreacted molecule itself is hazardous. As it has a negative impact on the biocompatibility (Yeom et al. 2010), the unreacted DVS needs to be removed by washing from the gel structure. Recently, new methods for the treatment of the DVS-polluted water were established. UV irradiation in presence of TiO_2 photocatalyst is capable of fully degrading the remains of the crosslinker (Marci et al. 2006). This method allows a more environmentally friendly application of the divinyl sulfone as the wastewater is reusable.

Epichlorohydrin (ECH) is another very significant crosslinking molecule. The reaction is similar to the divinyl sulfone as it needs alkaline environment to catalyze the reaction with the hydroxyl groups (McKelvey et al. 1963) (Fig. 2b). This makes it an excellent reagent for a wide array of polysaccharides. However, similarly to the DVS, its toxicity is a major disadvantage.

Crosslinking with glutaraldehyde and other dialdehydes is also a relatively common method due to their low toxicity. As the aldehyde groups can easily react with amine groups, it is usually used for the crosslinking of various proteins (Hopwood et al. 1970); thus, for the polysaccharides it is relatively rarely used with the exception of the chitosan, as the presence of amine groups makes it a perfect candidate for the reaction. However, the aldehyde groups can also react with the hydroxyl groups, leading to the formation of hemiacetal or even acetal if there is another nearby hydroxyl group (Tomihata and Ikada 1997b) (Fig. 2c). This requires acid component to catalyze the reaction, which is generally achieved with the addition of hydrochloric acid.

Carbodiimides are also primarily used to crosslink various polypeptides. The monomer, depending on the conditions, can easily react with a carboxyl groups and form an unstable intermediate which can then react with an amine (Nakajima and Ikada 1995). Unlike most crosslinking agents, the carbodiimide is a zero-length crosslinker: it only helps the crosslink formation between the two pendant groups, the crosslinking molecule itself is not part of the formed crosslink (Fig. 2d). As various carbodiimides are somewhat toxic, this is a big advantage as the removal of all crosslinkers after the gelation is possible. This makes it more favorable compared to other toxic molecules. They are usually used to crosslink carboxyl and amine groups, which is rarely exploitable for polysaccharides. However, the

Fig. 2 Crosslinking mechanism of divinyl sulfone (a), epichlorohydrin (b), glutaraldehyde (c), and carbodiimide (d)



carbodiimide can also be utilized to crosslink the chains with carboxyl and hydroxyl groups. After the reaction with a carboxyl group, the anhydride formation with another nearby carboxyl substituent is promoted, which is followed by a reaction with a hydroxyl group. This method was successfully applied for multiple polysaccharides, like hyaluronic acid (Tomihata and Ikada 1997a) and carboxymethylcellulose (Sannino et al. 2010).

The largest problem of the major crosslinking agents is their toxicity. Therefore, there is a considerable interest in the use of more environmentally friendly crosslinking agents like various polycarboxylic acids. Under normal conditions, the ester bond formation does not occur between the carboxyl and hydroxyl groups. However, if the polycarboxylic acid is dehydrated, the anhydride formed from two carboxyl groups can easily react with a hydroxyl pendant group (Fig. 3). The formation of anhydride is easily reached by heat treatment as even moderate temperatures (70–80 °C) promote the water loss. After esterification, one carboxyl group is freed up and it can participate in the anhydride formation with another nearby carboxyl group. Therefore, at least three carboxyl groups are required for the crosslinking effect. Due to the relatively low cost, the most important polycarboxylic acid is the citric acid which contains three carboxyl groups (Demitri et al.

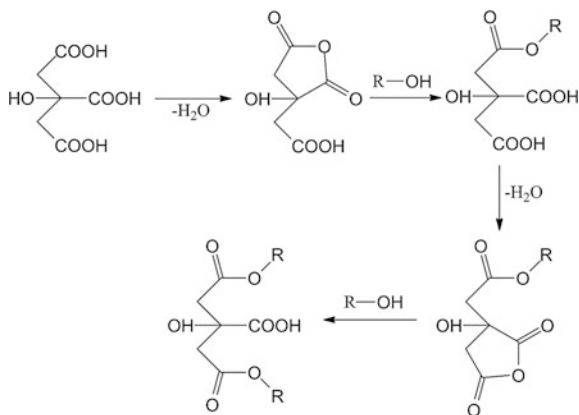
2008; Shi et al. 2008). However, the application of various tetracarboxylic acids was also investigated (Nazari et al. 2009). Usually, low temperatures and long treatment times are used. The latter is due to the water content of the solutions: the presence of the water molecules hinders the anhydride formation. The application of these green crosslinking agents was mostly investigated for the preparation of cellulose derivative gels, and in other areas like for fixation of cellulosic fiber structure in order to get crease resistant textiles.

The number of less common crosslinking agents is large. The crosslinking of *N*, *N'*-methylene-bis-acrylamide occurs through free-radical crosslinking; thus, it will be discussed in the next section. Other crosslinkers are rather specific and are used only for the crosslinking of certain polysaccharides; thus, they are reviewed in Sect. 5 under the subsection of the corresponding polymer.

4.2.2 Free-Radical Crosslinking

The crosslinking reactions can also occur through the highly reactive free radicals. The process requires initiation, which leads to the formation of the radicals. The radicals initiating the process are usually formed either during the degradation of the initiators or directly on the polymer chain by high energy irradiation. The radicals easily react with another macromolecule and the resulting product can also participate in further reactions. The reaction is terminated by the disproportionation or the combination of radicals. However, it is important to note that the radicals can not only initiate the crosslinking, but their reactions may also lead to chain scission, hindering the network formation. The relationship of the two processes heavily depends on various environmental parameters such as the presence of the solvent and the atmosphere, thus conditions favoring the crosslinking should be used. Crosslinking agents are also often introduced even for high energy irradiation to improve the crosslink formation, most common being the *N*, *N'*-methylene-bis-acrylamide.

Fig. 3 Crosslinking mechanism of citric acid



However, other monomers capable of gelation (network formation) such as acrylates are also often used.

The established method for the initiation is the addition of various chemical initiator systems (Ahmed 2015). The most common chemical initiators are the redox systems, most notable being persulfates (especially potassium (KPS) and ammonium (APS) persulfate). These agents are sensitive to the thermal degradation, thus elevated temperatures lead to the formation of radicals (Misra et al. 1984; Bao et al. 2011). The ionic interactions also affect the reaction mechanism as anionic radicals are the products of the degradation process. The macroradicals are formed through proton transfer to the sulfate radicals; the initiation requires acidic environment. Cerium ammonium nitrate is also a common chemical initiator: the Ce^{4+} cation forms a complex with the polysaccharide and the radicals are formed during its reduction to Ce^{3+} (Rahman et al. 2000). Similarly to the persulfate acidic medium is required, which is usually provided by the addition of nitric acid, although high acid concentration has a negative impact on the radical formation (Dhiman et al. 2008). While there are other common redox initiator systems, their importance in the synthesis of polysaccharide hydrogels is very small so far. The method is mainly used to prepare polysaccharide/acrylate copolymer hydrogels as the macroradicals easily react with molecules containing vinyl groups.

The formation of free-radicals can also be initiated by high energy irradiation. In these experiments usually gamma-irradiation or electron beam is used. In the first experiments regarding the irradiation of polysaccharide solutions only the degradation of the polymer was observed. However, Fei et al. (2000) discovered that the crosslink formation process becomes dominant when solutions with very high polymer concentration are irradiated. The macroradicals are formed by the cleavage of various chemical bonds in the structure. While a wide array of macroradicals can form, for the polysaccharides usually the C–H bonds are the most sensitive in the polymer backbone, leading to the highest radical yield. However, the presence of various pendant groups due to the derivatization also affects the process (Wach et al. 2003a, b). The gelation is heavily dependent on the molar properties such as the degree of substitution and the molecular weight. Moreover, besides the absorbed dose the dose rate is also an important factor as higher dose rates lead to better gelation. While the crosslink formation also occurs in air atmosphere, the presence of the oxygen hinders the process (Liu et al. 2002). Thus using vacuum or inert gas atmosphere helps the gelation as the free radicals do not react with oxygen. As solutions are used for the gelation, the solvent–irradiation interaction also affects the process. In aqueous solutions the radiolysis of water occurs, leading to the formation of reactive intermediates. These radicals can also attack the covalent bonds in the polymer (most important being the hydroxyl radicals), leading to the formation of macroradicals (Rosiak and Ulański 1999). The reactivity of these intermediates also shows large differences, the hydroxyl radicals showing significantly higher reactivity; moreover, the solution pH is also an important factor (Ulański and von Sonntag 2000; Wach et al. 2004).

UV irradiation is another possible route for the initiation. However, this method requires the addition of photoinitiators to the solution for the radical formation

(Fouassier and Lalevée 2012). Another common strategy is the functionalization of the polymer with chemical groups sensitive to the irradiation; for this methacrylation is the most popular choice (Smeds and Grinstaff 2001). Due to the smaller energy, UV irradiation allows in situ gelation without harmful effects, thus it is widely used in certain medical applications. However, for gels aimed at other fields the high energy irradiation shows higher potential.

4.3 Formation of Interpenetrating and Semi-interpenetrating Networks

If two or more polymers are present in the solution, different polymer networks can be formed depending on their chemical structure and the crosslinking method. Usually, the two components contain same reactive groups; thus, one crosslinking agent can react with both polymers. This method is the most common as it makes the crosslinking process much simpler. The polymers can also contain different groups which can react with each other, thus making the formation of the copolymer possible.

The two polymers do not need to be necessarily connected with covalent bonds, they can also form an interpenetrating network (IPN) structure (Dragan 2014). In this case, the polymer networks are not chemically crosslinked but their entanglement sterically prevents their separation. Such gels are usually synthesized in two steps where only one polymer is crosslinked in each step. This is most commonly achieved by the addition of two different crosslinking agents. However, as multiple polymers are present, gel can form even if a single component is crosslinked: the three-dimensional network forms the gel matrix, while the intermolecular interactions prevent the not crosslinked polymer component from leaving the gel structure during the swelling. Such structures are called semi-interpenetrating networks (semi-IPN). Similarly to the synthesis of IPN gels, crosslinking agents which react with a single component are needed for their preparation.

5 Polysaccharide-Based Hydrogels

While the aforementioned crosslinking strategies are widely used for polysaccharide systems, the importance of the individual methods shows a large difference depending on the type of the carbohydrate. Moreover, there is a wide array of other crosslinking routes which were only utilized for specific polymers so far, thus were not discussed previously. Therefore, in the following section, studies related to the gelation of different polysaccharide-based systems are reviewed separately, highlighting the specific considerations and unique methods for the various systems.

5.1 *Hydrogels Based on Cellulose and Its Derivatives*

5.1.1 Native Cellulose

Unmodified cellulose as a hydrogel material is widely studied due to its very low cost, but insolubility in water renders it less important than its derivatives. While chemically crosslinked gels were also prepared, the physical gelation has a much bigger role. The physical network is usually achieved by solvent exchange or temperature change. In the former method, water is used to disrupt the solvent–polymer interactions. Potthast et al. (2002a) investigated the behavior of cellulose dissolved in LiCl/DMAc and observed the slow aggregation of cellulose chains due to the hydrogen bonds. However, the presence of water even in very low concentrations led to the formation of larger aggregates. Ishii et al. (2006) prepared physical gels by two methods: coagulation with water and deionization with ion exchange resins. The addition of water led to instantaneous gel formation, while the slower deionization resulted in a more homogenous structure. Similar behavior was observed for tetrabutylammonium fluoride (TBAF)/DMSO solutions: the water disrupted the interaction between the hydroxyl groups of the cellulose and the fluoride; thus, intermolecular hydrogen bonds between the cellulose chains became dominant (Östlund et al. 2009). As very low water concentrations are required for the process, even the storage in humid environment is enough for the gelation of the solution (Patchan et al. 2013). The method is applicable for cellulose dissolved in ionic liquids, as well (Kadokawa et al. 2008).

The gelation can be induced by the change in the temperature, as well. Frey et al. (1996) studied the gelation of cellulose/ammonia/ammonium thiocyanate systems and observed that lower temperatures led to shorter gelling time. There is a much richer literature available about NaOH systems. Opposed to the ammonia/ammonium thiocyanate system, increasing the temperature was beneficial for the self-association of the cellulose in this solvent (Roy et al. 2003). Interestingly, lowering the temperature has a similar effect: Cai and Zhang (2006) studied the behavior of cellulose/NaOH/urea systems at different temperatures and noted that hydrophobic interactions between the cellulose chain become stronger at low temperatures (under 0 °C). LiOH-based systems were also used for the gelation of cellulose with higher molecular weight (Wang et al. 2013d). It is also important to note that unlike the physical gels of methylcellulose, the thermal gelation of the cellulose is an irreversible process under such conditions.

Epichlorohydrin (ECH) is the most common monomer for the chemical crosslinking of cellulose hydrogels. Westman and Lindström (1981) used cellulose xanthan as a precursor: the solution of the derivative was crosslinked with ECH, followed by regeneration with acid hydrolysis. However, recent studies focus on the direct crosslinking of cellulose. The method is similar to the physical gelation: cellulose is dissolved in NaOH/urea, stored in frozen state and after thawing the crosslinking agent is added. The chemical reaction occurs at room or slightly elevated temperature (Zhou et al. 2007). Chang et al. (2010b) also investigated the

effect of the post-treatment of the hydrogels: the samples were frozen or heated for 20 h. The former method resulted in better mechanical properties, while gels treated with the latter one had higher water uptake and better optical properties. There were also considerable efforts toward the copolymerization of cellulose with synthetic polymers. Chang et al. (2008) compared cellulose/PVA hydrogels both chemical gels with epichlorohydrin and physically crosslinked samples: the properties of the latter were inferior compared to the chemical gels. Wu et al. (2012a) used free-radical crosslinking to synthesize cellulose/acrylic acid/acrylamide hydrogels in the presence of MBA crosslinker. In a later work, Chang et al. (2011b) combined the two methods: after the gelation of cellulose with ECH, they prepared poly(*N*-isopropylacrylamide) (PNIPAAm)/cellulose gels by free-radical crosslinking the cellulose gel and the NIPAAm monomers.

5.1.2 Cellulose Derivatives

Unlike for most polysaccharides, the gelation of a wide array of derivatives is investigated for the cellulose. These polymers are cheap and have been used for a long time in the industry; thus, their properties are well known (Pappu et al. 2015, 2016). The literature focuses especially on the carboxymethylcellulose due to its advantageous properties, but other derivatives like the hydroxyalkyl, alkyl, and alkylhydroxyalkyl celluloses are also common subjects of the studies.

Carboxymethylcellulose hydrogels

The carboxymethyl derivatives of cellulose and other polysaccharides are a popular choice for the gel formation due to their excellent swelling properties. This is related to the carboxyl groups which are deprotonated at nonacidic pH: the electrostatic repulsion helps the expansion of the gel network which leads to better swelling (Barbucci et al. 2000). The process is affected by the Donnan effect, as well: the charged carboxyl groups and their counterions result in a high ion concentration in the hydrogel compared to the solvent environment. This leads to an osmotic effect promoting the diffusion of the water into the gel structure. These effects also mean that the carboxymethylcellulose hydrogels are highly sensitive to the environmental conditions, such as the pH and the ionic strength, while having higher water uptake than hydrogels based on alkyl and hydroxyalkyl derivatives of cellulose (Fekete et al. 2014).

Studies related to the physical gelation of carboxymethylcellulose are relatively limited. The easiest route is the complexation with multivalent cations. While the ionic crosslinking was also used for pure carboxymethylcellulose solutions (Saglam et al. 2002), it is much more prevalent in the synthesis of copolymer gels with other natural polymers containing anionic groups, most notably being alginate. For these blends CaCl_2 , the classic crosslinker for alginate-based gels is widely used (Mai et al. 2013; Ren et al. 2016), but exchanging it to the salts of various trivalent ions such as Fe^{3+} and Al^{3+} leads to a stronger structure (Nie et al. 2004; Kim et al. 2012; Swamy and Yun 2015). However, the importance of the complexation is small compared to the chemical crosslinking of the cellulose derivative.

Chemical gelation of carboxymethylcellulose with crosslinking agents is the most established strategy. The classic crosslinkers for the derivative are the epichlorohydrin and the divinyl sulfone. While both reagents are capable of crosslinking pure carboxymethylcellulose solution, the electrostatic repulsion between the chains hinders the crosslinking, leading to the formation of intramolecular crosslinks. However, by introducing a nonionic polymer such as the hydroxyethylcellulose, the intermolecular reactions are easier and the gelation improves significantly (Anbergen and Oppermann 1990; Esposito et al. 1996). In such systems, not only the interaction between the carboxyl groups is weaker, but also the nonionic polymer is not affected by the charged groups; thus, it easily participates in the crosslinking process.

In recent studies, the interest is shifted toward the more environmentally friendly crosslinking agents. The polycarboxylic acids are major contenders in this field. Besides the low toxicity, mild synthesis conditions are sufficient and some of these reagents are relatively cheap. The first experiments involved the application of citric acid as crosslinking agent (Demitri et al. 2008), but recently other polycarboxylic acids like succinic acid, maleic acid (Hashem et al. 2013), and 1,2,3,4-butanetetracarboxylic acid (Nazari et al. 2009) were also used for the crosslinking. Fumaric acid is also viable reagent; however, unlike other polycarboxylic acids, it requires highly acidic environment (Akar et al. 2012). The crosslinking is initiated by a mild heat treatment at 70–80 °C. Similarly to the toxic crosslinkers, the presence of nonionic cellulose derivatives improves the crosslink formation. The gel properties can be changed by implementing post-treatment after the crosslinking: Hashem et al. (2013) improved the gelation by a second short, high-temperature curing step after mild heating. Besides carboxylic acids, carbodiimide was also successfully utilized as a green crosslinker due to the zero-length linkages (Sannino et al. 2010). The reaction requires acidic initiation, which was provided by dilute citric acid solution.

Free-radical chemical crosslinking is also a common way for the preparation of carboxymethylcellulose gels. Generally, ammonium persulfate is used as a chemical initiator in the presence of *N,N'*-methylene-bis-acrylamide (MBA) crosslinking agent. However, chemical initiation is mostly used for the synthesis of copolymer gels with synthetic polymers. For pure carboxymethylcellulose solutions, the initiation by high-energy irradiation is the preferred method.

High-energy irradiation is an excellent way to prepare chemically crosslinked carboxymethylcellulose gels without any additives. While pure carboxymethyl hydrogels are synthesized from aqueous solutions, for the synthesis of copolymer gels other solvents are also used if the other polymer is insoluble in water (Tang et al. 2014). The crosslink formation requires relatively high solute concentrations as in dilute solutions the degradation processes dominate due to the hindering effect of the electrostatic repulsion (Fei et al. 2000). The critical concentration also depends on several factors such as the degree of substitution. Moreover, recently Wach et al. (2014) also successfully prepared hydrogels with dilute solutions. The native pH of the CMC-Na solution is slightly alkaline; thus, the carboxyl groups are deprotonated and the electrostatic repulsion between them hinders the crosslink

formation. Shifting the pH toward acidic character led to the protonation of the carboxyl groups and the lack of interaction between them promoted the gelation. Several other factors such as the storage time before the irradiation (Wach et al. 2000) also affected the gel fraction. Liu et al. (2002) observed that not only the lack of oxygen leads to better gelation, but the type of the inert atmosphere also has an impact on the process. The radiation-initiated crosslinking can be further improved by adding crosslinking agents in low concentrations. While they are used mostly for the synthesis of copolymer gels, they can also improve the gelation of pure cellulose derivative solutions (Fekete et al. 2016a). In their presence, the crosslinking requires significantly milder conditions and better gel properties can be achieved than for the crosslinker-free hydrogels.

Methylcellulose hydrogels

The most important representative of the alkylcelluloses is the methylcellulose. It is a major additive in the food industry, where its thermogelling behavior is also utilized to affect the baking of pastes (Sanz et al. 2004). The gelation mechanism of the methylcellulose is explained with the interaction of the hydrophobic methyl substituents (Sarkar 1979). At low temperatures, the hydrophobic interactions are hindered by the hydration of the polymer chains; however, increasing the temperature leads to lower hydration, thus the interactions between the methyl groups are less obstructed. Haque and Morris (1993) attributed the gelation also to the changes in the solution structure. During the derivatization of the cellulose, the crystalline structure is not completely destroyed; thus, small aggregates are present in the methylcellulose solution. However, at high temperatures, the aggregates are partly broken up and the free ends of the polymer chains forming the aggregates also become more mobile. The degree of substitution and the distribution of the substituents also affect the gelling behavior. Higher degree of substitution leads to lower gel temperature due to the higher number of hydrophobic groups. This also explains the importance of the distribution of the substituents: the regions with higher degree of substitution play a larger role in the gelation than other regions (Desbrières et al. 1998). High molecular weight is also beneficial for the process, leading to a shift toward lower gelation temperatures (Takahashi et al. 2001). The required temperature can also be altered by chemical modification: Liu et al. (2004) prepared *N*-isopropylacrylamide/methylcellulose copolymers, where the ratio of the two components determined the gelation temperature.

The chemical gelation of methylcellulose holds a relatively small significance due to the importance of the thermal gelation. Chemically crosslinked hydrogels of methylcellulose were prepared through free-radical crosslinking: Wach et al. (2003a) crosslinked concentrated methylcellulose solutions by high-energy irradiation. They found electron beam significantly more efficient than gamma irradiation, leading to higher gelation. Methylcellulose gels showed good swelling properties but were inferior to hydroxyethylcellulose-based hydrogels due to the hydrophobic pendant groups. Photoinitiated crosslinking also proved to be a viable route, but in this case, acrylate was also present in the system besides the photoinitiator. Aouada et al. (2009) synthesized methylcellulose/polyacrylamide copolymer gels in presence of

MBA crosslinking agent. The application of previously modified methylcellulose was also investigated: Stalling et al. (2009) used methacrylated methylcellulose for photoinitiated gelation. The modified cellulose derivative was prepared by reaction of the polymer with methacrylic acid anhydride. Rimdusit et al. (2012) also compared high-energy irradiation and crosslinking with glutaraldehyde: while the presence of the crosslinking agent also led to gelation, the properties proved to be inferior compared to the irradiation-crosslinked gels.

Hydroxyalkylcellulose-based hydrogels

Hydroxyethylcellulose and hydroxypropylcellulose are the hydroxyalkylcellulose with the largest industrial application; thus, unsurprisingly studies of gelation are also limited to these two derivatives. While there are more studies related to the synthesis of chemical gels, their thermal behavior was also examined (Klug 1971). Heating the aqueous solutions of hydroxyalkylcelluloses promotes the aggregation through the hydrophobic interactions. However, unlike the methylcellulose, this process leads to precipitation due to the phase separation instead of gel formation.

The chemical crosslinking of hydroxyalkylcelluloses is usually achieved by divinyl sulfone crosslinker. Chemical gels of hydroxyethylcellulose were mostly prepared in the presence of another polymer component. In copolymer hydrogels with carboxymethylcellulose, the role of the HEC was to promote the intermolecular crosslinking (Anbergen and Oppermann 1990). A similar method was used for the synthesis of copolymers with hyaluronic acid (Kwon et al. 2015) and gelatin (Kajjari et al. 2011); in the latter case, glutaraldehyde was utilized instead of divinyl sulfone. On the other hand, hydroxypropylcellulose gels were also prepared without the addition of a second polymer. Besides DVS, other crosslinkers like epichlorohydrin were also used (Yan et al. 2009). Another strategy for the synthesis of hydrogel nanoparticles is the temperature-induced aggregation: increasing the temperature led to the formation of small aggregates, where the polymer chains can be crosslinked chemically in a second step (Gao et al. 2001). However, the phase transition does not necessarily need the change of the temperature: by introducing surfactant (Lu et al. 2000) or electrolyte (Xia et al. 2003) into the cellulose derivative system the water-polymer interactions become weaker and aggregation occurs at lower temperature.

Free-radical crosslinking is usually initiated by UV irradiation. First studies involved the synthesis of hydroxypropylcellulose hydrogels either after chemical modification (Marsano et al. 2000) or in the presence of a synthetic polymer (Marsano and Bianchi 2002). Later the focus is shifted toward the pure cellulose derivative systems. Petrov et al. (2006) investigated the cryotropic gelation of hydroxypropylcellulose. Aqueous solutions of the polymer and the photoinitiator were frozen which led to phase separation. The formation of the frozen solvent fraction leads to high polymer concentration in the other phase; thus, the crosslinking processes of the free radicals become dominant opposed to the degradation. This made possible the gelation even in semi-dilute solutions. In a later study, the method was successfully utilized for the gelation of hydroxyethylcellulose, as well (Petrov et al. 2007). Moreover, they observed that the radical formation also occurs in the presence of hydrogen peroxide (a common chemical

redox initiator with Fe^{2+}). This allowed the substitution of the (4-benzoylbenzyl) trimethylammonium chloride photoinitiator with a more environmentally friendly additive.

High-energy irradiation was used for initiation to a lesser extent. Both hydroxyalkylcelluloses formed gels when their concentrated solutions were irradiated (Wach et al. a, b). The dependence of the properties on the synthesis parameters was similar to the carboxymethylcellulose systems. Moreover, the introduction of low concentrations of MBA crosslinker had a positive impact on the gel formation (Fekete et al. 2016a).

Alkylhydroxyalkylcellulose-based hydrogels

The gelation of alkylhydroxyalkylcelluloses was investigated only for two representatives: the hydroxypropylmethylcellulose and the ethylhydroxyethylcellulose. Similarly to the methylcellulose, the physical crosslinking by heat treatment shows a large importance due to the industrial applications. However, the hydrogel synthesis of the two derivatives was investigated at somewhat different conditions. For the hydroxypropylmethylcellulose, the thermal gelation is very similar to the behavior of the methylcellulose due to the methyl substituents in both derivatives (Sarkar 1979). On the other hand, the presence of the hydroxypropyl groups hinders the gelation process, leading to higher gelation temperature. This is attributed to two effects: the hydroxypropyl groups are less hydrophobic than the methyl groups and the larger substituents also sterically interfere with the formation of the hydrophobic ordered structures (Haque et al. 1993).

The thermal behavior of the ethylhydroxyethylcellulose is quite different. Its aqueous solution shows a decrease in the viscosity with the temperature. Above the cloud point phase, separation occurs, leading to even lower viscosity. However, the presence of ionic surfactants significantly alters this process: the hydrophobic polymer–surfactant interactions promote the formation of the polymer–polymer interactions, leading to the formation of physical gels (Carlsson et al. 1990). The effect also heavily depends on the type of the surfactant as depending on the chemical structure it interacts differently with the polymer chains (Nyström and Lindman 1995; Wang and Olofsson 1995).

Pure cellulose derivative chemical gels were only prepared from hydroxypropylmethylcellulose. Pekel et al. (2004) used gamma irradiation to crosslink HPMC solution. The swelling of the gels was sensitive to the pH and the temperature. The sensitivity was further improved by introducing phthalate groups into the polymer structure (Xu et al. 2002b). However, the phthalate derivative has low solubility in water; thus, it requires the addition of Na_2CO_3 for full dissolution.

5.2 Hydrogels Based on Starch and Its Derivatives

The application of starch as a hydrogel material is less widely studied than the other major polysaccharides. Moreover, studies focus on the use of starch as a copolymer

instead of the preparation of pure starch hydrogels. Usually, various reactive monomers like acrylic acid or acrylamide are added to starch (Kiatkamjornwong et al. 2000), but polyvinyl alcohol and other synthetic polymers with relatively low molecular weight are also used (Pal et al. 2006). The dispersion of the other components is achieved through the pregelatinization of the aqueous dispersion of starch, which results in a highly viscous solution due to the improved swelling of the granules. The gelation occurs through free-radical crosslinking; both chemical initiator systems like potassium persulfate/KOH (Xiao and Yang 2006) and high-energy irradiation (Zhai et al. 2002) are widely used for the initiation. The process can be further improved by introducing other crosslinking agents, *N,N'*-methylene-bis-acrylamide being the most common choice. While the crosslinking through free radicals is by far the most important method, there were efforts to crosslink starch systems through chemical reactions, as well. The gel properties are not only determined by the synthesis parameters, but the properties of the starch also play a major role. The starch source not only affects the amylose/amylopectin ratio but also the concentration of other minor components, like the lipids; the amylose/amylopectin ratio is an especially important factor during the crosslinking process. Zhai et al. (2002) prepared PVA copolymer gels with pure amylose and amylopectin besides cornstarch. Amylose-based systems showed significantly better properties as the polyvinyl-alcohol reacted more easily with the amylose than the amylopectin. Pal et al. (2006) synthesized starch/poly(vinyl alcohol) crosslinking copolymer hydrogel membranes with glutaraldehyde as a crosslinker.

Carboxymethylation of starch offers a different route to the gelation due to the water solubility. Nagasawa et al. (2004) synthesized superabsorbent gels from aqueous solutions of carboxymethylstarch. Similarly to the water-soluble derivatives of cellulose, the gelation improved significantly with the increasing solute concentration, but led to worse swelling properties. Separate study of carboxymethylated amylose and amylopectin proved that the amylopectin ratio was a determining factor in gel formation of the derivatives, but the tendency is reversed compared to the non-modified starch described earlier: in the presence of PVA, the branched amylopectin gelled even at relatively low solute concentrations, while the amylose showed gelling behavior only at 50 wt% concentration.

5.3 Hydrogels Based on Chitin and Its Derivatives

5.3.1 Chitin

Precipitation is a common method for the preparation of chitin hydrogels due to the water insolubility of the polymer: chitin is dissolved by one of its solvents and the solution is slowly added to a water bath. The dissolution is usually achieved by CaCl_2 /methanol solvent system (Tamura et al. 2006; Nagahama et al. 2008), but in some experiments hydrogels were prepared from chitin dissolved in NaOH/urea by freeze-drying (Chang et al. 2011a) and in DMA/LiCl systems (Tsiptsias and

Panayiotou 2008), as well. There is also a large interest regarding the composites from physically crosslinked chitin gels, where the nanoparticles are incorporated into the gel structure after the precipitation. As the application of chitin-based physical gels is centered on the medical field, achieving antibacterial activity by silver (Madhumathi et al. 2010) or metal oxide (Kumar et al. 2013) particles is widely studied.

Multiple crosslinking strategies were examined for the preparation of chemically crosslinked networks. Tang et al. (2012) crosslinked dissolved chitosan with epichlorohydrin through the hydroxyl groups. NaOH/urea was used as solvent which also provided the alkaline environment required for the reaction. Epichlorohydrin was also utilized for the preparation of chitin-based copolymer gel with carboxymethylcellulose (Tang et al. 2014) and composite with hydroxyapatite (Chang et al. 2013).

Crosslinking with the more environmentally friendly polycarboxylic acids was also studied. Yoshimura et al. (2005) used succinic anhydride to crosslink chitosan solution: the acid anhydride reacted with the hydroxyl groups of the chitin. Moreover, the free carboxyl group formed after the reaction could also react with another hydroxyl group. The solvent present during the crosslinking had a major effect on the gelation: in DMSO/TBAF solutions, the chemical crosslinks easily formed, while in LiCl/*N*-methyl-2-pyrrolidone (NMP) solutions, the second reaction was inhibited; thus, minimal gelation was observed. Opposed to the polycarboxylic acids, the use of anhydride and the lack of water allowed bypassing the heat treatment. Kono and Zakimi (2013) synthesized gels with the dianhydride of butanetetracarboxylic acid from blends of chitin and cellulose in LiCl/NMP. The two anhydride groups allowed the formation of crosslinks despite the free carboxyl groups not participating in the crosslinking. However, the presence of non-reacted carboxyl groups led to responsive behavior: unlike the native polymers, the copolymer exhibited sensitivity to the pH of the environment.

5.3.2 Chitosan

Chitosan-based physical gels are prepared either by various additives which interact with the chitosan chains or by chemical modification. In the latter case, new functional groups are introduced into the polymer structure by grafting; thus, the gel formation can occur through new mechanisms. Qu et al. (1999) prepared lactic acid modified chitosan through heat treatment. The lactic acid reacted with the amine group, which was followed by polyesterification. The formation of the physical gel was attributed to the hydrophobic interactions between the substituents and the hydrogen bonds. By introducing hydrophobic groups thermoreversible gelling can be also achieved: grafting chitosan with poly(ethylene glycol) led to a water-soluble chitosan derivative, but at higher temperature, the stronger hydrophobic interactions resulted in physical gelation (Bhattarai et al. 2005). Freeze-thawing is also a possible method for gelation: Yang et al. (2008) prepared PVA/chitosan solution by multiple freeze-thaw cycles at $-20\text{ }^{\circ}\text{C}$.

The second strategy for the physical gelation is the introduction of various additives to the chitosan solution. These can also induce the thermal gelation of the solution through hydrophobic interactions. Such behavior was observed in the presence of polyols. Chenite et al. (2001) used β -glycerophosphate disodium salt to neutralize the chitosan solution, leading to thermogelating systems at body temperature. Other polyols exhibited similar effect on the chitosan systems (Schuetz et al. 2008). Chitosan gels grafted with monomers of thermosensitive polymers like *N*-isopropylacrylamide exhibited similar behavior (Chen and Cheng 2006). The gelation is often achieved through ionic interactions, as well. This requires the presence of polymers with negative charges which can interact with amine groups in the chitosan backbone. As anionic polymers are relatively common in the nature, most studies focus on the application of various natural polymers for the synthesis as a cheap, green alternative to synthetic polymers (Berger et al. 2004). While polymers with carboxyl groups are the most common choice, the addition of polysaccharides containing sulfate or phosphate groups is also a viable route.

Glutaraldehyde is a common chemical crosslinker for chitosan as the aldehyde groups easily react with the amines (Mirzaei et al. 2013). However, the crosslink formation can be initiated by a single aldehyde group, as well. Singh et al. (2006a) utilized formaldehyde to gelate chitosan solution at acidic pH. The reaction of the formaldehyde and the amine pedant group resulted in the formation of imine which in acidic environment can react with a second amine, thus forming a crosslink. A more environmental friendly alternative is the genipin due to its low toxicity, which is isolated from gardenia fruits. The molecule with a carboxyl and two hydroxyl groups does not only react with the amine groups to form crosslinks, but its homopolymerization is also observed (Mi et al. 2000). The pH has a major effect on the reaction. Alkaline environment promotes the formation of homopolymer chains; thus, long crosslinks are formed between the chitosan macromolecules. On the other hand, in acidic environment, the crosslinks are short (dimers, trimers, and tetramers of genipin), and the more compact gel structure leads to worse swelling properties (Mi et al. 2005).

Free-radical crosslinking is usually initiated by UV irradiation. Ono et al. (1999) prepared water-soluble photocrosslinkable chitosan by reacting chitosan with azide (p-azidobenzoic acid) and lactose (lactobionic acid). The introduction of lactose groups improved the solubility in water; thus, aqueous solutions formed even at neutral pH. On the other hand, the azide group is sensitive to the UV irradiation, leading to the formation of reactive nitrene group which reacts with another nitrene or a free amine group to form azo crosslinks.

Vinyl groups are also commonly introduced for easier crosslink formation. Hong et al. (2006) achieved this by grafting methacrylic acid on chitosan, while grafted lactic acid provided the water solubility. The crosslinking reaction was initiated via ammonium persulfate and *N,N,N',N'*-tetramethylethylenediamine redox system. Due to the fast gelation at body temperature, these gels show large potential as injectable hydrogels.

High-energy irradiation also proved to be suitable for the gelation of chitosan. Yang et al. (2008) synthesized chitosan/poly(vinyl alcohol) gels by gamma

irradiation. While the gels showed high water uptake, the mechanical properties were poor. However, irradiated samples treated with freeze-thawing had higher mechanical strength.

5.3.3 Derivatives of Chitin and Chitosan

Hydrogels based on water-soluble derivatives of chitin have a relatively small literature. Zhao et al. (2001) modified chitin by carboxylation: the carboxymethylated derivative was water soluble and was crosslinked with chitosan in aqueous solution with glutaraldehyde. The formed copolymer had better properties than the gels synthesized from either derivative. Zhao et al. (2003a, b) also prepared hydrogels from carboxymethylated derivatives of chitin and chitosan by high-energy irradiation. Similarly to the cellulose derivatives, by irradiating high concentrated solutions no additives were required for the gelation. Gels of both derivatives had good swelling properties and carboxymethylchitosan gels also exhibited antibacterial activity.

Similarly to the chitin, carboxymethylated of chitosan is the only chitosan derivative for which the hydrogel formation was studied. Pure carboxymethylchitosan hydrogels were prepared from aqueous solutions with glutaraldehyde by Zamani et al. (2010). The drying method after the crosslinking was also a determining factor for the swelling behavior: freeze-drying and foaming with pentane resulted in porous gels with very high water uptake compared to oven-drying. Bidgoli et al. (2010) also investigated the effect of the carboxymethylation: the water uptake improved with the concentration of the carboxyl groups; thus, higher degree of substitution was favorable for the synthesis of superabsorbents. Carboxymethylchitosan-based copolymer gels were also investigated: besides the copolymers formed with chitin discussed previously (Zhao et al. 2003a), gelatin was also used to prepare green hydrogels. The solution of the two polymers was crosslinked by gamma irradiation; thus, no additives were needed (Yang et al. 2010).

5.4 Hydrogels Based on Alginate

The crosslinking of alginate systems has a wide literature, the most important gelation method being the complex formation with multivalent ions. The application of divalent cations was extensively studied, from which the calcium cation has the largest significance. The interaction between the Ca^{2+} and the alginate chains leads to the formation of an egg-box structure, where the cations are surrounded by the polymer layers (Grant et al. 1973). The calcium complexes are still held a large importance due to the easily achieved gelation and are widely used especially in medical fields. The calcium source has a major effect on the gelation. Usually, CaCl_2 is used due to its good water solubility and fast crosslink formation. While

short gelation times are preferred in the practice, too fast gelation can lead to an inhomogeneous structure. Calcium salts with low solubility like CaCO_3 allow an even distribution of the cations at the expense of slower gelation, leading to homogeneous gel (Kuo and Ma 2001). A major disadvantage of the Ca-alginate gels is the low stability which leads to cation release during application (Ng and Cheng 2007); thus, the applicability of other divalent ions like Fe^{2+} (Kroll et al. 1996), Sr^{2+} , Ba^{2+} , and Zn^{2+} (Yang et al. 2013; Harper et al. 2014) was also investigated: the cation type had a significant effect on the gel properties. Interestingly, while Mg^{2+} is often considered as a non-gelling cation, in very high ion concentrations (5–10 times higher than for Ca^{2+}) in fact it is capable of crosslinking the alginate; however, the gelation is very slow compared to other multivalent cations (Topuz et al. 2012). Trivalent ions also show a large potential as they can interact stronger with the alginate, leading to faster gelation and a more stable structure. Rochefort et al. (1986) investigated the effect of the treatment of weakly crosslinked Ca-alginate with $\text{Al}(\text{NO}_3)_3$ solution. The presence of the Al^{3+} ions led to a significant improvement in the gelation. Al-alginate complexes can also form without a pre-crosslinking step with calcium ions. Banerjee et al. (2013) prepared alginate/methylcellulose hydrogels where the Al-complex provided the gel structure. Depending on the other components in copolymer systems, the cations can also interact with the other polymer: in alginate/carboxymethylxanthan systems, the cations interacted with both polymers due to the carboxyl groups (Ray et al. 2011). Menakbi et al. (2016) also investigated the complexation of several trivalent cations like Sc^{3+} , Cr^{3+} , and La^{3+} . The binding strength depended on the cation, but in all cases, it was stronger than for the divalent cations.

While the ionic crosslinking with multivalent cations is a simple method, it also has disadvantages like the sensitivity to the presence of non-crosslinking ions. Therefore, other possible crosslinking paths were also investigated. Physical crosslinking can be achieved alternatively by modifying the chemical structure of the alginate so new interactions appear between the chains. Boisseson et al. (2004) introduced long alkyl chains through substitution: the hydrophobic interaction between the alkyl chains resulted in a gel stable in the presence of ions, although complexing multivalent cations further improved the stability of the network structure.

Alginate gels crosslinked with covalent bonds were also prepared both by chemical crosslinking agents and free-radical crosslinking. In the former case, both the hydroxyl and carboxyl groups can participate in the crosslink formation depending on the crosslinking agent. Crosslinkers containing amine groups can easily react with the carboxyl groups. Moreover, derivatives of hydrophilic polymers like poly(ethylene glycol) used as crosslinking agents also improve the swelling of the gels (Lee et al. 2000a). On the other hand, glutaraldehyde crosslinks alginate by reacting with the hydroxyl groups in acidic environment (Kulkarni et al. 2000). Kim et al. (2000b) also used this agent to synthesize alginate-based gel fibers. Water-soluble carbodiimides as zero-length crosslinking agents were used to form crosslinks between the hydroxyl and carboxyl groups of the alginate (Xu et al. 2002a).

Free-radical crosslinking is also a viable strategy for the gel formation. It is mostly used for the preparation of alginate-based composite or copolymer gels. Chemical initiation is generally used for the radical formation: ammonium persulfate is added as initiator, while MBA monomer participates in the crosslinking. Copolymer gels with other polymers like carboxymethylcellulose (Pourjavadi et al. 2006) were also prepared, but most studies focus on the synthesis of alginate/clay composites (Yadav and Rhee 2012). For photoinitiated crosslinking only the gelation of methacrylated alginate was studied (Jeon et al. 2009; Smeds and Grinstaff 2001). While radiation-initiated crosslinking was also used for the synthesis of alginate/methacrylate copolymer gels (Bardajee et al. 2012), currently its significance is still very small.

5.5 Hydrogels Based on Hyaluronic Acid

Studies focus solely on the chemical gelation of the hyaluronic acid. The crosslinking routes are somewhat different than for the other polysaccharides: hyaluronic acid is usually chemically modified by the introduction of new pendant groups before the gelation. However, the gelation of unmodified hyaluronic acid was also studied to a smaller extent. First experiments involved crosslinking with glutaraldehyde (Tomihata and Ikada 1997b); the removal of solvent by freeze-drying led to a porous chemical gel structure (Collins and Birkinshaw 2011). Divinyl sulfone is another classic crosslinker which was first utilized for the preparation of cellulose derivative/hyaluronic acid hydrogels (Sannino et al. 2004). However, later the focus is shifted to the crosslinking of pure hyaluronic acid systems. Collins and Birkinshaw (2008) compared the gelation by DVS, glutaraldehyde, and freeze-thawing. Covalently crosslinked systems showed better mechanical properties than the physical gels; moreover, the crosslinking efficiency of the two molecules also differed as the addition of glutaraldehyde led to higher crosslink density. It is also important to note that high DVS concentration has a negative impact on the cytocompatibility, which is a crucial factor for medical applications (Lai 2014). Ibrahim et al. (2010) also observed that the modification of gel properties is possible through addition of hyaluronic acid oligomers. Carbodiimides also play an important role in the synthesis of hyaluronic acid gels: during the chemical modification of the carboxyl groups, the introduction of the new functional groups is often carried out with its utilization due to the zero-length crosslinking. However, the direct crosslinking of the polysaccharide is also feasible with crosslinking agents containing multiple amine groups: Jeon et al. (2007) used this method to prepare hyaluronic acid/polyethylene-glycol copolymer gels by crosslinking hyaluronan with the diamine derivative of PEG. Carbodiimide crosslinker was also utilized for the crosslinking of pure hyaluronan through esterification (Tomihata and Ikada 1997a).

As discussed above, there is an even larger interest toward the use of chemically modified hyaluronic acids. These newly introduced functional groups are not only

the participants of the crosslinking process but also affect the gel properties. Even the formation of autocrosslinkable hyaluronic acid gels is possible, where the presence of air is adequate to initiate the gelation: through the oxidation of thiol groups by the oxygen disulfide crosslinks form between the macromolecules (Shu et al. 2002). The rate of the crosslink formation can be increased by the addition of crosslinkers which easily react with thiols such as the α,β -unsaturated esters and amides of poly(ethylene glycol) (Shu et al. 2004). A large variety of substituents were investigated, typically molecules containing hydrazide, thiol, or aldehyde groups (Burdick and Prestwich 2011). Acryloyl groups are especially popular as they are not only capable to react with certain groups like thiols (Hahn et al. 2006) but also allow the free-radical crosslinking of the polymer. Most commonly methacrylate groups are introduced through the functionalization with glycidyl methacrylate (Leach et al. 2003) or methacrylic anhydride (Burdick et al. 2005), but other acrylates are also often utilized (Sahoo et al. 2008). The formation of free radicals is usually initiated by UV irradiation in the presence of photoinitiators; the application of redox initiators is rarely used. The degree of substitution has a major impact on the gel properties: Bencherif et al. (2008) noted that the crosslink density increased with the degree of methacrylation, leading to better mechanical properties at the expense of lower water uptake. To promote the crosslink formation, co-monomers such as *N*-vinyl-2-pyrrolidone (NVP) are also sometimes added to the functionalized hyaluronic acid (Patterson et al. 2010).

5.6 Hydrogels Based on Other Polysaccharides

While gelation of the aforementioned polysaccharides is in the center of interest, studies do not focus solely on them. However, while other polysaccharides are widely used in industrial applications as additives, their importance in the gel preparation is so far much smaller than for the above-mentioned, more common polysaccharides. Therefore, only a short overview is given on them.

5.6.1 Dextran

Dextran are a group water-soluble polysaccharides consisting of a backbone of D-glucose groups with $\alpha(1 \rightarrow 6)$ and/or $\alpha(1 \rightarrow 3)$ linkages, with branches in different positions; they are produced from glucose by bacterial fermentation. Chemical gels from unmodified dextran were prepared with various crosslinkers such as diisocyanates (Hovgaard and Brønsted 1995) or sodium trimetaphosphate (Wintgens et al. 2015); moreover, even enzymatic crosslinking with divinyl adipate crosslinker was achieved (Ferreira et al. 2005). However, the polysaccharide is also very often functionalized. After carboxymethylation, the chemical gelation of the derivative can be carried out with carbodiimides, thus forming zero-length crosslinks (Zhang et al. 2005c). Its dialdehyde derivative is applicable for

copolymerization with polymers containing amine groups like gelatin (Draye et al. 1998) or chitosan (Gómez-Mascaraque et al. 2014); the synthesis of pure dextran hydrogels is also possible with adipic acid dihydrazide modification (Maia et al. 2005). Methacrylated dextran is easily crosslinked in presence of chemical initiator through free-radical crosslinking (van Dijk-Wolthuis et al. 1997). Moreover, the acrylated (Kim et al. 1999) and methacrylated (Kim and Chu 2000) derivatives are used for the formation of photocrosslinkable hydrogels.

5.6.2 Agarose

Agarose is a linear polysaccharide extracted from seaweeds consisting of alternating D-galactose and 3,6-anhydro-L-galactose units with $\alpha(1 \rightarrow 3)$ and $\beta(1 \rightarrow 4)$ linkages. While it is not water soluble at room temperature, it readily dissolves in hot water. Cooling its solution leads to thermoreversible gel formation. Most studies involving such systems focused on its application for the controlled release of various bioactive molecules (Wang and Wu 1997; Meilander et al. 2003; Liu and Li 2005; Liang et al. 2006), incorporation of nanoparticles (Luo et al. 2016; Wang et al. 2016) and gel electrophoresis (Serwer 1983). Chemical gels with citric acid (Awadhiya et al. 2016) and epichlorohydrin (Zhang et al. 2012) were also prepared, but their importance is much smaller compared to the more convenient thermal gelation.

5.6.3 Xanthan

Xanthan is a water-soluble heteropolysaccharide with a $\beta(1 \rightarrow 4)$ linked D-glucose backbone and side chains consisting of D-glucuronic acid and D-mannose containing acetyl and pyruvate groups; it is produced from carbohydrates by bacterial fermentation. Despite its good water solubility, physical gels can be prepared by annealing (change in the ordered structure) at high temperature and subsequent cooling its aqueous solution (Quinn et al. 1994). The presence of charged groups allows the ionic crosslinking of the polymers with multivalent cations (Izawa et al. 2009) or cationic polymers like chitosan (Dumitriu et al. 1994; Chellat et al. 2000). Chemical crosslinking is also viable with molecules containing amine groups in the presence of carbodiimide (Bejenariu et al. 2008). For the chemical crosslinking of xanthan solution, a number of crosslinking agents are applicable, such as epichlorohydrin (Alupej et al. 2002), citric acid (Bueno et al. 2013), and trisodium trimetaphosphate (Bejenariu et al. 2009). There is also a large interest toward free-radical copolymerization with various acrylates and methacrylates (Gils et al. 2009; Kulkarni and Sa 2009a; Mittal et al. 2014).

5.6.4 Chondroitin Sulfate

Chondroitin sulfate is a linear polymer with alternating D-glucuronic acid and N-acetyl-D-galactosamine units with sulfate residues; it is extracted from cartilage

of various animals. Due to its water solubility, mainly the chemical gelation was investigated. While pure chondroitin sulfate gels can be prepared with crosslinkers like ethylene glycol diglycidyl ether (Jensen et al. 2002), most studies focus on the synthesis of copolymer hydrogels with various natural and synthetic polymers. The chondroitin sulfate functionalization with *N*-hydroxysuccinimide (Strehin et al. 2010), adipic acid dihydrazide (Gilbert et al. 2004; Zhang et al. 2011b), methacrylates (Bryant et al. 2004; Li et al. 2004), or through oxidation (Dawlee et al. 2005) is carried out for the covalent crosslinking with the other polymer component even for systems capable of forming ionic complexes like chondroitin sulfate/gelatin solutions (Kuijpers et al. 2000). The copolymerization can also occur without functionalization with appropriate crosslinkers like epichlorohydrin (Oprea et al. (2012).

5.6.5 Other Polysaccharides

A wide array of other polysaccharides like the guar gum (Das et al. 2006), tara gum (Huang et al. 2007, Abd Alla et al. 2012), tragacanth gum (Singh and Sharma 2014), carrageenan (Xu et al. 2003), lignin (Thakur and Thakur 2015), pectin (Sutar et al. 2008), hemicellulose (Gabrieli and Gatenholm 1998), and psyllium polysaccharide (Thakur and Thakur 2014) were also investigated to a lesser extent for the hydrogel formation. Sometimes their pure solution is also used for gel formation (especially for thermogelling polymers), but usually, they are added as a natural component for the copolymerization with synthetic polymers, although rarely they are also mixed with natural polymers to modify their properties.

6 Copolymer and Composite Hydrogels

The modification of hydrogels by introducing another component is very common; mixing polysaccharides and synthetic polymers has a large literature due to their importance in the practical use. However, there is also a major interest in the blends and copolymers with other natural polymers to keep them more environmentally friendly. Another interesting strategy is the incorporation of inorganic components in the gel network, either to reduce the costs or achieve novel properties. In the following, these three types of modifications are in-depth reviewed.

6.1 Blends and Copolymers with Other Natural Polymers

A green route to modify the properties of the polysaccharide hydrogels is the introduction of other natural polymers instead of synthetic ones. This allows achieving novel properties without the application of nonrenewable materials.

A large part of such studies focuses on the blends and copolymers of different polysaccharides due to the similarities in the chemical structure. However, the modification with other major natural polymers used for hydrogel synthesis such as collagen also plays an important role.

6.1.1 Hydrogels Based on Multiple Polysaccharides

The introduction of another polysaccharide can serve multiple purposes. The preparation of blends allows the modification of the hydrogel properties without the introduction of additives or synthetic components; thus, the hydrogels keep the advantageous properties of polysaccharides, such as the good biocompatibility, biodegradability, and the sole use of renewable materials. While similarities such as the presence of hydroxyl groups offer a convenient route for the crosslinking of different polymers, the different functional groups also allow the preparation of semi-IPN and IPN hydrogels through separate polymer networks (Chen et al. 2004).

Despite the larger importance of chemical crosslinking, physical hydrogels were also in-depth investigated. Thermal crosslinking of these blends is rare, as thermogelling systems are usually modified with various additives or by grafting monomers of thermosensitive synthetic polymers. On the other hand, precipitation and ionic crosslinking are commonly utilized for these systems. The former method is usually used if both polymers are insoluble in water, like the blends of cellulose, chitin, and chitosan (Sun et al. 2009; Liu et al. 2012). In such cases, solvents capable of dissolving all components like ionic liquids are required. If one of the polymers is water soluble, usually a post-crosslinking step is used to make the hydrogel more stable (Chiaoprakobkij et al. 2011).

Ionic interactions are also very important for the crosslinking of multiple polysaccharides. Not only several native polysaccharides contain charged (mainly carboxyl) groups, but the carboxymethylation is a common derivatization method for the nonionic polymers, as well. In such systems, the use of multivalent cations is very popular as they interact with all polymers containing anionic pendant groups. The most common component for these hydrogels is the alginate, which is mixed with other anionic polymers (Lin et al. 2005; Kim et al. 2012; Tran et al. 2013). Chitosan is also an important polymer due to its cationic character. As the protonated amino groups can interact with the carboxyl groups of an anionic polymer, the formation of polyionic hydrogel system occurs without the need of complexing ions (George and Abraham 2006).

The chemical crosslinking of different polysaccharides is carried out relatively easily due to the similarities in the functional groups. Certain crosslinking agents like divinyl sulfone (Sannino et al. 2004), epichlorohydrin (Chang et al. 2009, 2010a) or polycarboxylic acids (Kono and Zakimi 2013) react with the hydroxyl groups; thus, they are widely used for crosslinking different polysaccharides. Crosslinkers containing aldehyde groups also need a special mention: besides the application of common crosslinkers like glutaraldehyde (Işiklan 2006), the aldehyde groups are also often introduced into the polymer component through

oxidation; thus, they fulfill the function of the crosslinker (Li et al. 2012b). Nonionic polymers are often used to improve the gelation: while the electrostatic repulsion between polymer chains containing charged groups hinders the crosslinking process, the nonionic component is not affected by it; thus, the crosslinks form more easily between the macromolecules. Hydroxyethylcellulose is a good example as it is often utilized to help the crosslink formation of carboxymethylcellulose systems (Demitri et al. 2008).

6.1.2 Carbohydrate/Amino Acid-Based Hydrogels

Collagen-based blend and copolymer hydrogels

Polypeptides form the other major group of natural polymers. For the modification of polysaccharide hydrogels, collagen is their most important representative. It is insoluble in water, but slightly acidic pH is sufficient for its dissolution. While several different types of collagen are present in animals, studies related to the hydrogel synthesis investigate mainly the application of collagen I, the most common one, an important component of skin, tendon, and bone. Studies focus mainly on its utilization with hyaluronic acid and chitosan; the interest toward blends and copolymers with other polysaccharides is much smaller. The largest attention toward such copolymer structures is shown in the field of tissue engineering for the preparation of hydrogel scaffolds.

Methods used for the synthesis of hyaluronic acid/collagen hydrogels show a large variety. Besides covalently crosslinking the two polymers, the formation of semi-IPN and IPN structures is also common. Semi-interpenetrating network is often achieved by the methacrylation of hyaluronic acid, leading to photocrosslinkable semi-IPN hydrogels (Brigham et al. 2009). Such systems are advantageous for the preparation of injectable hydrogels crosslinkable in situ with UV irradiation (Omlor et al. 2012). If this property is not required, the addition of chemical crosslinkers like poly(ethylene glycol) diglycidyl ether (PEGDGE) is also a viable strategy if the collagen is added after the crosslinking in a separate step (Kim et al. 2007). However, the collagen component can also form the three-dimensional network through self-assembly (fibrillogenesis) (Harris et al. 2013). Both processes can be simultaneously utilized, leading to IPN hydrogels with superior mechanical properties compared to the semi-IPN structures (Suri and Schmidt 2009). Composite hydrogels were also utilized by adding collagen fibers prepared by electrospinning into hyaluronic acid/gelatin solution during the gelation process (Ekaputra et al. 2011). For chemical crosslinking of the two polymers, carbodiimide is an excellent crosslinker due to the presence of carboxyl and amine groups (Park et al. 2003; Kim et al. 2008c). PEGDGE can be also utilized if the agent is added when both polymers are present in the solution (Segura et al. 2005b).

Chitosan is another popular choice for the copolymer synthesis. For chemical gelation, crosslinking agents capable of reacting with the amino groups present in

both polymers are generally used. While mostly glutaraldehyde is utilized (Wu et al. 2007), other less common crosslinkers containing aldehyde groups such as glyoxal (Wang and Stegemann 2011) or formaldehyde (Zhang et al. 1997) are also used to a lesser extent. Other agents like genipin (Yan et al. 2010) and carbodiimide/*N*-hydroxysuccinimide system (Rafat et al. 2008; Deng et al. 2010) were likewise utilized in some studies; the latter one was also used to crosslink hydrogels based on collagen and the carboxymethyl derivative of chitosan (Chen et al. 2006). The physical gelation is usually achieved by incubation at 37 °C to promote the formation of the fibrous structure of collagen, while the chitosan is aggregated with the increase of the pH (Tan et al. 2001; Chiu and Radisic 2011; Reis et al. 2012). There is a major interest in the preparation of systems capable of thermal gelation, as well. Most studies investigated chitosan/ β -glycerophosphate systems where the addition of collagen has a beneficial effect on several properties: such systems not only gel faster, but they show lower cytotoxicity and slower degradation (Song et al. 2010; Wang and Stegemann 2010; Li et al. 2012a). As even body temperature is sufficient for the thermal gelation, these properties make such systems an excellent material for injectable hydrogels in the medical field.

In case of cellulose-based copolymers, most commonly the native (especially bacterial) cellulose is used as a second polymer with collagen. Due to the poor water solubility of the components, the preparation of physical gels is very common. Two different strategies were utilized: either the two polymers were dissolved simultaneously and then precipitated (Wang et al. 2013b), or the prepared cellulose gel is immersed in the collagen solution to allow its absorption and interaction with the cellulose chains (Zhijiang and Guang 2011). Chemical crosslinking of the two components is also possible through chemical modification: Saska et al. (2012) used amino acid or its derivative to modify the polysaccharide, which then covalently reacted with the collagen in presence of carbodiimide crosslinker. This zero-length crosslinker was also utilized for the solution of carboxymethyl derivative of cellulose and collagen in presence of adipic acid dihydrazide (Liu et al. 2013). On the other hand, Cheng et al. (2014) directly introduced aldehyde groups into the cellulose structure through oxidation, which then reacted with the amine groups of the collagen.

The literature regarding alginate/collagen hydrogels is even more limited, despite the complexation of alginate with multivalent cations allowing easy formation of physical composite gels (de Cunha et al. 2014). Moreover, similarly to the carboxymethylcellulose, the chemical crosslinking of the two polymers with carbodiimide is also possible due to the presence of carboxyl pendant groups on the alginate chain (Liu et al. 2008b).

Gelatin-based blend and copolymer hydrogels

While non-modified collagen is widely used, there is an even larger interest in the utilization of gelatin, the product of the degradation or denaturation of collagen. Unlike the original polymer, gelatin is soluble in water over 30 °C and cooling its solution leads to the formation of physical gels (Eldridge and Ferry 1954; Hayashi and Oh 1983). While chemical crosslinking strategies used for the collagen gelation

are also applicable for the gelation, due to its larger importance the utilized methods are much more diverse. Similarly to the collagen, the most commonly used copolymer polysaccharides are the hyaluronic acid and the chitosan, but there is a major interest in alginate/gelatin systems and mixing with starch, cellulose, and its derivatives, as well.

For the synthesis of hyaluronic acid/gelatin hydrogels, the chemical gelation is utilized in most studies. Similarly to hyaluronic acid/collagen copolymers, carbodiimides are the usual chemical crosslinking agents (Zhang et al. 2011a; Zhou et al. 2013a, b). Derivatization is another common approach for the chemical gelation. Unlike the collagen-based gels, gelatin is also modified along with the hyaluronic acid component; thus, both polymers participate in the chemical gelation. Methacrylation is very common to prepare autocrosslinkable hydrogels (Skardal et al. 2010; Camci-Unal et al. 2013), but reagents containing thiol groups are also often used to modify both polymers, which then react with each other to form disulfide crosslinks when exposed to air (Shu et al. 2003). Moreover, the introduction of crosslinkers like derivatives of poly(ethylene glycol) does not only increase the gelation rate of the thiolated derivatives, but it also offers a convenient way to modify the gel properties (Mironov et al. 2005; Vanderhoogz et al. 2009). Enzymatic crosslinking was also used to a lesser extent: Crescenzi et al. (2002) utilized transglutaminase-catalyzed copolymerization after the modification of hyaluronan with dipeptide.

Physical gels of chitosan and gelatin are prepared in multiple steps: the two components are dissolved separately by adding acid or heating, the two solutions are mixed, followed by cooling and neutralization (Chang et al. 2002; Nagahama et al. 2009). For crosslinking through the amine groups, several crosslinking agents were utilized, such as glutaraldehyde (Yao et al. 1995; Zhao et al. 2002; Franco et al. 2011), genipin (Cui et al. 2014), and proanthocyanidins (Kim et al. 2005). They are usually added to the polymer solution, but the immersion of physical gels in the crosslinker solution is also possible (Shen et al. 2000). Carbodiimides are also applicable, although in this case only gelatin has the carboxyl groups required for the crosslink formation; thus, the chitosan chains are not directly crosslinked (Gorgieva and Kokol 2012). The molecule was utilized for the synthesis of hyaluronic acid/chitosan/gelatin hydrogels, as well (Tan et al. 2009). Enzymatic crosslinking catalyzed by transglutaminase is also more advantageous for copolymerization with chitosan than for hyaluronic acid/gelatin systems, as the former polysaccharide does not require functionalization due to the amine groups (Chen et al. 2003). Besides the chitosan its carboxymethyl derivative was also used for the copolymerization: Yang et al. (2010) utilized gamma irradiation to initiate the free-radical crosslinking. Moreover, gelatin-based composite hydrogels containing chitin nanofibers showed excellent mechanical properties (Hassanzadeh et al. 2016).

While combining alginate with collagen was barely studied, the use of its denatured form was in-depth investigated. Like for other polysaccharide/gelatin systems, glutaraldehyde is commonly utilized as a chemical crosslinker for semi-IPN hydrogels (Dong et al. 2006; Liu and Zhao 2006). The addition of Ca^{2+}

cations is also often used to achieve IPN structures from semi-IPN through the ionic crosslinking of alginate (Fadnavis et al. 2003). Another interesting approach is the enzymatic crosslinking of gelatin instead of the addition of classic crosslinker molecules (Wen et al. 2014). Moreover, IPN structure was also observed under the sol-gel temperature of gelatin: in this case, both polymers form physical networks (Awad et al. 2004; Duan et al. 2013). The major strategy for the covalent crosslinking of the polymers is the derivatization of alginate through oxidation, which then reacts with the amine groups in presence of catalyst (usually borax) (Balakrishnan et al. 2005); the application of such hydrogels is widely investigated as scaffolds in tissue engineering. Another possible route is the addition of carbodiimide for the formation of amide groups (Yang et al. 2009). Aroguz et al. (2014) used a two-step crosslinking process: first crosslinked oxidized alginate with adipic dihydrazide and in the following step, the gelatin was added with the carbodiimide. The modified alginate can also function as a crosslinker: Sakai et al. (2008) prepared Ca-alginate/gelatin hydrogel fibers, which were then immersed into a solution containing oxidized alginate to crosslink the gelatin component, as well.

The application of native cellulose with gelatin is more limited compared to the collagen. Nakayama et al. (2004) prepared IPN structures by chemically crosslinking gelatin with carbodiimide, while the cellulose formed a separate physical network. On the other hand, Dash et al. (2013) used oxidized cellulose nanowhiskers to covalently crosslink the gelatin solution. However, there is also an interest toward the use of cellulose derivatives; in these experiments, the formation of IPN hydrogels was carried out by the addition of glutaraldehyde crosslinker. This method was used for the gelation of solutions formed with the carboxymethyl (Rathna et al. 1996; Rokhade et al. 2006) and hydroxyethyl (Kajjari et al. 2011) derivatives of cellulose, as well.

For starch-based systems, physical gelation is the standard route for the gel formation. Elevated temperatures, sufficient not only for the gelatin dissolution but also for the gelatinization of the starch, are used in this process (Abdulmola et al. 1996). Besides the ratio of two polymers, the starch type also has a major impact on the gel properties (Mallick et al. 2014). Porous gels were also prepared from such systems: Jaya et al. (2009) used microwave vacuum drying as a more efficient method compared to freeze-drying for starch/gelatin/hydroxyapatite composites.

Copolymers based on other amino acid-based polymers

Other polypeptides like albumin were also utilized to a very small extent. Tada et al. (2007) chemically crosslinked alginate with albumin in presence of carbodiimide crosslinker; thus, the polypeptide formed the crosslinks between the polysaccharide chains. On the other hand, Boppana et al. (2010) prepared IPN hydrogel from carboxymethylcellulose and albumin: multivalent cations were used for the physical crosslinking of the cellulose derivative, while albumin was crosslinked with glutaraldehyde. Interestingly, oligopeptides were also capable to crosslink functionalized dextran to form hydrogels (Lévesque and Shoichet 2007).

6.2 Grafting and Copolymerization with Synthetic Polymers

The literature related to synthetic polymer-based hydrogels is vast compared to the polysaccharide gels. Therefore, unsurprisingly there are numerous studies related to the preparation of their blends and copolymers. The ratio of the polysaccharide and synthetic polymer content used in the studies show a large variety, but the amount of the synthetic component is usually considerable, often higher than polysaccharide content. Thus, investigations focus on the blends and copolymers with the most important commercial polymers.

6.2.1 Acrylates and Methacrylates

Most commercial products are based on acrylates due to their low cost and advantageous properties like responsivity to various environmental conditions. Therefore, it is not surprising that the copolymers formed with acrylates are the most widely studied. The first studies involved the application of acrylic acid for the copolymer gel formation with chitosan: a large advantage over the other polysaccharides is the presence of amine groups, as in charged form they can interact with the carboxyl groups of the acrylic acid depending on the pH. Such copolymers were prepared by Wang et al. (1997) first: the chitosan was chemically crosslinked with glutaraldehyde, while the poly(acrylic acid) was bound by the electrostatic interaction. Moreover, the chemical crosslinking of chitosan is not required for the formation of such physical gels (de la Torre et al. 2003). While in this case the acrylic acid was added as a polymer, in most studies its monomer is used instead. Chemical initiators (Yazdani-Pedram et al. 2000), UV (Lee et al. 1999) and high-energy irradiation (Shim and Nho 2003) are all common methods to initiate the reactions of the acrylic acid. Hydrogels by grafting acrylic acid on chitin (Tanodekaew et al. 2004) and alginate (Yin et al. 2008) were also prepared, but currently their importance is very small. As for the cellulose, only its carboxymethyl derivative was gelled in presence of the acrylic acid (Bajpai and Mishra 2004; Zhang et al. 2014a). In most studies very high acrylic acid content is used compared to the polysaccharide; however, very low amount of acrylic acid can be also utilized to improve the gelation of the polysaccharide solution. This leads to not only better gel properties but also milder synthesis conditions are required (Fekete et al. 2016b).

Acrylamide is another common acrylic monomer; its polymerization is likewise achieved through free radicals. Similarly to the acrylic acid, copolymerization with chitosan was in-depth studied (Risbud and Bhone 2000; Kumbhar et al. 2003; Xia et al. 2005). While usually chemical initiator/MBA crosslinker systems are used, Sokker et al. (2011) also achieved gel formation by high-energy irradiation in the absence of the crosslinking agent. The irradiation method is also common for the carboxymethylcellulose/acrylamide systems; while MBA monomer is often used to improve the gelation (El-Din et al. 2010; Hemvichian et al. 2014), crosslinker-free

gels were also synthesized (Abd El-Mohdy 2007). Alternatively, the carboxyl groups of the cellulose derivative allow the preparation of semi-IPN gels by multivalent cations with polyacrylamide (Aalaie et al. 2013). Alginate/acrylamide gels also have considerable literature; such gels are synthesized in two-step crosslinking: acrylamide is crosslinked by free-radical crosslinking, while multivalent cations are added for the complexation of the alginate (Omidian et al. 2006). Ca^{2+} cations are usually used as a crosslinker, but better mechanical properties can be reached through their replacement with trivalent ions (Yang et al. 2013). Moreover, free-radical crosslinking alone is also capable of crosslinking alginate/acrylamide solutions (Kulkarni and Sa 2009b). An interesting method to accelerate the process is microwave irradiation: Singh et al. (2006b) observed that the gelation was significantly faster and low initiator content and air atmosphere proved to be adequate.

While both acrylic acid and acrylamide are widely used separately for copolymerization as discussed above, the copolymer of the two is also common due to the excellent swelling properties related to the presence of both amine and carboxyl groups. Their first polysaccharide-based copolymers were prepared with starch via free-radical grafting (Athawale and Lele 2000; Kiatkamjornwong et al. 2000). The ratio of the two monomers had a major impact on the water uptake: the use of their mixtures led to better swelling properties than when only one of them was added. Acrylic acid-co-acrylamide gels were prepared with several polysaccharides such as cellulose (Wu et al. 2012a), chitosan (Mahdavinia et al. 2004), and their derivatives (Suo et al. 2007; Yin et al. 2007). Alginate-based copolymers were also synthesized: in this case, crosslinking with multivalent cations was also utilized next to the chemical crosslinking (Yahşi et al. 2005). Other components like methacrylates (Li 2010) or clay minerals (Rashidzadeh et al. 2014) are also commonly introduced to improve the properties. While the acrylamide and acrylic acid is mostly added in monomer form, other synthesis routes are also available: Sadeghi and Hosseinzadeh (2007) copolymerized CMC and polyacrylonitrile (PAN); the amino and carboxyl groups were formed by the alkaline hydrolysis of PAN in presence of ammonia.

An even more intensively studied monomer is the *N*-isopropylacrylamide (NIPAAm) as its thermosensitivity even at low temperatures makes it an excellent candidate for medical hydrogels. Copolymer and IPN hydrogels formed with alginate and chitosan have the largest literature. The former polysaccharide is used mostly for the preparation of IPN structures achieved by free-radical crosslinking of the alginate/NIPAAm solution, followed by complexation of the alginate with Ca^{2+} cations (Guilherme et al. 2005; Petrusic et al. 2012). Semi-IPN structures are also attainable: Ju et al. (2002) and Shi et al. (2006) used the polymer of the acrylamide derivative to prepare ionically crosslinked alginate/PNIPAAm solution: the physically crosslinked alginate matrix bound the acrylate chains through weak interactions. However, the alginate does not necessarily form the crosslinked network: if only the free-radical crosslinking of the mixture solution is carried out, then the covalently crosslinked network is formed by the PNIPAAm (Zhang et al. 2005a; Dumitriu et al. 2010). Semi-IPN gels show better swelling properties than their full-IPN counterparts, but the deswelling is slower (Lee et al. 2006). Functionalization also offers another route to chemically crosslink the two

polymers: Ju et al. (2001) introduced amine groups to the PNIPAAm polymer which the Ca-alginate in the presence of carbodiimide.

For chitosan-based hydrogels, the synthesis of semi-IPN structure by crosslinking the NIPAAm monomer is the most common route (Wang et al. 2000; Verestiuc et al. 2004). If full interpenetrating network is the goal, then glutaraldehyde crosslinking agent is added after the first polymerization step (Lee and Chen 2001; Alvarez-Lorenzo et al. 2005). Grafting offers an alternative for gels with different properties: the monomer is grafted on the chitosan and the modified polysaccharide forms the three-dimensional network (Kim et al. 2000a; Lee et al. 2004a; Cai et al. 2005). Such gels also exhibit thermal sensitivity due to the acrylate side chains. The crosslinking method affects the gel properties, as well: grafted copolymer gels show better responsivity to the environmental parameters at the expense of lower water uptake compared to IPN hydrogels (Kim et al. 2000a). Grafting glycidyl methacrylate in a second step to the polymer backbone leads to photocrosslinkable systems—this property is utilized for the formation of injectable hydrogels in medicine (Zhang et al. 2014b). Similarly to the alginate, the chemical reaction of the two components is also a viable route for grafting, but in this case, the PNIPAAm is functionalized with reagents containing carboxyl groups (Lee et al. 2004b; Chen and Cheng 2006). NIPAAm is also often used with carboxymethylchitosan as such gels have better pH-sensitivity compared to copolymers containing unmodified chitosan (Guo and Gao 2007; Ma et al. 2007a, b).

While first studies of cellulose/NIPAAm systems involved the modification of cotton fibers by radiation-initiated grafting (Jun et al. 2001), in later experiments, hydrogels were also synthesized by free-radical crosslinking (Gupta and Khandekar 2003; Wang et al. 2013c). Cellulose derivatives were also utilized for the modification of the PNIPAAm gels: the copolymerization with carboxymethylcellulose leads to pH and thermosensitive systems (Ma et al. 2007b; Ekici 2011), while the thermal sensitivity can be changed with hydroxypropyl (Chauhan et al. 2004; Xu et al. 2010) and methyl (Liu et al. 2010) derivatives. Grafting with *N*-isopropylacrylamide is also an interesting route to prepare thermosensitive hyaluronic acid gels as the polysaccharide component has minimal effect on the thermal behavior of NIPAAm (Ohya et al. 2001). Polymerization of the synthetic monomer in presence of the hyaluronan is also a common strategy for formation of semi-IPN structure (Santos et al. 2010; Coronado et al. 2011).

Copolymerization is not limited to the aforementioned monomers. Methacrylate monomers such as the hydroxyethylmethacrylate (Mandal and Ray 2013), 2-dimethylaminoethylmethacrylate (Salama et al. 2016), and alkylmethacrylates (Li 2010) were also used among other acrylate and methacrylate components. However, their crosslinking mechanism is very similar to the one discussed for the above-mentioned monomers and their importance is very small; thus, they will not be further discussed.

6.2.2 Polyvinylpyrrolidone

Synthetic polymers other than acrylates are also widely used for the copolymerization with polysaccharides. Other common synthetic polymers, especially ones widely applied in the medical field, are also investigated to achieve better properties than the homopolymer gels. Polyvinylpyrrolidone is a popular material for hydrogel synthesis as its thermosensitivity is very advantageous in the medicine similarly to the PNIPAAm. However, the relatively low swelling and poor mechanical properties (especially fragility) led to the investigation of its copolymers to counter these disadvantages, for which polysaccharides also proved to be effective besides the usual acrylate copolymers (Wang et al. 2007). While in some studies the monomer of the PVP was added to the solution (Işıklan et al. 2008), usually its polymer with varying molecular weight is utilized. There is an especially large focus on chitosan/PVP hydrogels; in earlier studies, semi-IPN gels were synthesized by chemically crosslinking the chitosan with glutaraldehyde (Risbud et al. 2001; Risbud and Bhat 2001) or genipin (Khurma et al. 2005). However, recently the interest shifted toward the radiation-induced crosslinking (Nho and Park 2002; Dergunov et al. 2005; Archana et al. 2013). The latter method was also used for the copolymers formed with carboxymethylchitosan (Zhao et al. 2006), starch (Zhai et al. 2002), and alginate (Singh and Singh 2012), as well. For the latter polysaccharide, complexation was also utilized for the preparation of physical gels (Doria-Serrano et al. 2002). Out of the cellulose-based copolymer gels, the major focus is on the carboxymethylcellulose (Wang et al. 2007; Lü et al. 2010); besides the chemical crosslinking, heat treatment under pressure similarly proved to be a viable method for physical gel formation (Roy et al. 2010). The addition of hydroxypropyl (Marsano and Bianchi 2002) and methylhydroxyethyl (Plungpongpan et al. 2013) derivatives of cellulose also had a positive impact on the properties of PVP gels. PVP is also a frequent copolymer for less studied polysaccharides like pectin (Mishra et al. 2008) and κ -carrageenan (Relleve et al. 1999; Abad et al. 2003) in the hydrogel formation.

6.2.3 Poly(Vinyl Alcohol)

Poly(vinyl alcohol) (PVA) is a popular hydrogel material for biomedical applications due to its excellent biocompatibility. For polysaccharide/PVA systems, the physical gelation holds larger importance than the chemical crosslinking as it can be easily achieved via freeze-thawing the PVA solution (Yokoyama et al. 1986); this is often utilized for the polysaccharide/PVA blends, as well. The gelation method also heavily depends on the polysaccharide type; the most common copolymer for PVA being the chitosan. Physical gels are prepared by both freeze-thawing and elevated temperatures. The former route is widely used (Sung et al. 2010), despite the presence of chitosan hindering the association of the PVA molecules in frozen state, leading to a weaker structure (Cascone et al. 1999). On the other hand, at high temperatures, the stronger hydrophobic interactions between the polymer chains

lead to the gel formation (Minoura et al. 1998). Moreover, while heat treatment at higher temperatures is common (Koyano et al. 1998; Jin and Bai 2002; Zhu et al. 2012), the gelation may occur under body temperature or even room temperature depending on the ratio of the components, making it ideal for medical applications (Tang et al. 2007). Chemical gels were also prepared by various methods, such as the addition of glutaraldehyde (Wang et al. 2004b; Costa-Júnior et al. 2009; Kumar et al. 2009), ethylene glycol diglycidyl ether (Liu et al. 2010), UV (Kim et al. 2003), or gamma irradiation (Nho and Park 2002). Yang et al. (2008) combined freeze-thawing and irradiation: they observed that even the order of the two crosslinking steps affected significantly the gel properties. Besides chitosan, its carboxymethylated derivative was also used for the formation of physical (Lee et al. 2009) and chemical (Zhao et al. 2003b) gels with PVA. For starch/PVA systems, the pregelatinization of the starch is generally utilized. While films were also prepared through pure physical crosslinking by heat treatment (Spiridon et al. 2008; Tang et al. 2008), for the hydrogel synthesis, the pregelatinized systems are also chemically crosslinked in the following step. This is achieved with crosslinkers capable of reacting with hydroxyl groups like citric acid (Shi et al. 2008) or formaldehyde (Han et al. 2009); free-radical crosslinking initiated with gamma irradiation is another possible way to avoid the use of such additives (Zhai et al. 2002). Interestingly, physical gels were also prepared by freeze-thawing after grafting PVA onto the starch backbone (Xiao and Yang 2006). Studies involving unmodified cellulose hydrogels focused on its physical gelation by the freezing method (Millon and Wan 2006; Chang et al. 2008). On the other hand, for the carboxymethyl derivative physical (Barkhordari et al. 2014), chemical crosslinking (Taleb et al. 2009; Rao et al. 2012) and a mixture of the two steps (El-Salmawi 2007) were also examined. So far there was only minor interest in other cellulose derivatives, although Park et al. (2001) studied the gelation of methylcellulose/PVA solutions in presence of glutaraldehyde. For hyaluronic acid-based copolymers, both physical crosslinking with freeze-thawing (Guerra et al. 1994) and chemical gelation with glutaraldehyde (Kim et al. 2004) were investigated.

6.2.4 Poly(Ethylene Glycol)

Poly(ethylene glycol) (PEG) (also known as polyethylene oxide (PEO), although it is usually used for its high molecular weight variant) is another common material for hydrogel formation. Unlike the above-mentioned polymers, it is mainly utilized as a spacer macromolecule; this allows the formation of longer and more mobile crosslinks, leading to better swelling properties. Most studies involve the application of low molecular weight PEG, but gelation with large spacer molecules (over 10^5 Da) was also reported (El-Din et al. 2013). As PEG does not react directly with the polysaccharides, the addition of various crosslinking agents or chemical modification is required. The most common crosslinker for this purpose is the divinyl sulfone. The chemical crosslinking can occur in the simultaneous presence of all three components (Esposito et al. 2005), but the polyethylene-glycol can be

previously functionalized through reaction with DVS, as well (Jin et al. 2010). Likewise, PEG is also often chemically modified with various reagents to make the direct reaction with the polysaccharide possible. The diglycidyl ether of PEG is an excellent crosslinker due to the reactive epoxy groups (Kono 2014). Another good example is the introduction of amine groups which in the presence of carbodiimide crosslinker easily react with polymer containing carboxyl groups, such as the alginate (Eiselt et al. 1999) or hyaluronic acid (Jeon et al. 2007). UV-initiated crosslinking is a viable strategy if vinyl groups are present in the polymer—this is usually achieved by various acrylates (Leach and Schmidt 2005; Zhong et al. 2010). In such systems, both PEG and the polysaccharide are modified to contain double bonds. The two components can also be functionalized using different groups which easily react with each other: Shu et al. (2004) used thiolated hyaluronic acid and PEG modified with various acrylates for chemical crosslinking. If only PEG is functionalized, hydrogels with interpenetrating network can be prepared; this is especially characteristic for chitosan/PEG systems, where the chitosan is cross-linked with glutaraldehyde, while the reaction of the acrylated PEG is initiated by UV irradiation (Lee et al. 2000b; Kaewpirom and Boonsang 2006). The gelation is often carried out by high-energy irradiation, as well; this allows the crosslinking without the functionalization of the polymers due to the free radical formation. This strategy was utilized for carboxymethylcellulose/PEG copolymer hydrogels (Lee et al. 2005; El-Din et al. 2013).

6.3 Composite Hydrogels with Inorganic Components

Recently, there are major efforts for the use of various inorganic materials for the preparation of composite gels. Studies focus on two major groups of inorganic components: clays and metal nanoparticles. The application of the two groups is fueled by very different goals. Clays are very cheap resources available in abundance. While their presence also modifies the gel properties, the main reason for their use is to reduce the costs of the gel preparation. On the other hand, the aim of the metal nanoparticle incorporation is the introduction of novel properties, such as the antibacterial behavior. The mineral content of the composites shows a large variety: in some experiments, only very low amounts of it are added, while in others the inorganic content is over 50%.

6.3.1 Minerals

Studies investigating the incorporation of minerals in polysaccharide hydrogels show a huge variety in the type of the added inorganic component. While the goal is the reduction of the production costs by lowering the polysaccharide content, it is a major requirement that the inorganic component should not negatively affect the swelling properties. Therefore, the polymer is generally mixed with materials

containing hydrophilic pendant groups like silicates or double layered hydroxides. The mineral component is added in powder form to the solution before the crosslinking process; the particle size is usually under 100 μm , but several experiments use particles even in the nanometer range as this allows the formation of homogeneous dispersions.

The most important minerals with hydrophilic properties are the silicates, where the hydrophilic surface is provided by the silanol groups. Studies focus on the application of various aluminosilicate clay minerals such as the kaolinite (Pourjavadi et al. 2007), montmorillonite (Liu et al. 2008a), palygorskite (also known as attapulgite) (Wang et al. 2009), illite (Wang et al. 2013f), and vermiculite (Xie and Wang 2009). Kaolinite is mostly added in the form of kaolin (kaolinite-rich clay), but other minerals are mainly used as pure minerals, although the use of bentonite (rich in montmorillonite) instead of pure montmorillonite is also common (Oh et al. 2011). Other silicates like mica minerals, sericite being their most important representative, are utilized to a lesser extent, as well (Wu et al. 2000). Earlier studies involved the modification of polysaccharide/acrylate copolymers to further reduce the production costs. Due to the acrylate component, the gelation is carried out by free-radical crosslinking; this also allows the formation of covalent bonds between the mineral and the polymer besides the weak interaction of the components. While most studies use chemical initiators, gamma irradiation also proved to be a viable route (El Salmawi and Ibrahim 2011). Wu et al. (2000, 2003) investigated the effect of the addition of three types of clays (kaolin, bentonite, and sericite) on the gel properties in starch/acrylamide systems. The mineral not only made the synthesis more cost-effective, but it also led to improved swelling at low mineral concentration. However, very high silicate content had a negative impact on the water uptake. The mineral type also proved to be an important parameter as the differences in the hydration affected the crosslinking process. The synthesis of superabsorbent polysaccharide/acrylate/mineral composites was accomplished with other natural polymers such as the cellulose (Anidhuran et al. 2011), chitosan (Xie and Wang 2009), alginate (Pourjavadi et al. 2007), and guar gum (Wang and Wang 2009), as well. Moreover, there are also recent studies involving the gelation of the carboxymethyl (Wang and Wang 2010; Bao et al. 2011) and methyl (Bortolin et al. 2013) derivatives of cellulose in composite systems.

Despite the large interest in the copolymer composite gels, pure polysaccharide/mineral composites offer an alternative way to prepare cheaper and more environmentally friendly gels. Alginate is a popular choice due to the easy physical crosslinking via complexation. The first such system was prepared by Céspedes et al. (2007) with the addition of CaCl_2 to alginate/clay solutions, while Singh et al. (2009b) further introduced starch into the alginate/clay system. Their method was similar but hot water was required in the latter case to form a homogeneous solution due to the presence of starch. Besides the alginate, chitosan was also utilized to form physical gels with montmorillonite (Celis et al. 2012). Chemical crosslinking is also a viable strategy for such composites: Yang et al. (2012) synthesized alginate/modified rectorite composites by free-radical crosslinking initiated by potassium persulfate in presence of *N,N'*-methylene-bis-acrylamide crosslinker.

While minerals are usually added in their natural form to lower the production costs, the chemical modification of clays is also an interesting approach to adjust their properties depending on the application field. So far, only the organic modification (achieved through the replacement of cations with molecules containing hydrophobic groups like cationic surfactants) is relevant for the hydrogels, especially in case of montmorillonite. The change in the structure leads to a more hydrophobic character which hinders the gelation process (Xu et al. 2006). However, this property can be utilized in the water treatment: the hydrophobic interactions participate in the adsorption of certain pollutants, leading to higher adsorption capacity (Wang and Wang 2013). Recently, organically modified illite was also employed for the preparation of composite gels with alginate for dye adsorption (Wang et al. 2013g).

Double layered hydroxides (DLH) have a very different structure compared to the silicates. The cations form a layer structure which is surrounded by the anions and other molecules like water. Hydrotalcite is the most often used native mineral, but synthetic double layered hydroxides are also significant. The multivalent ions present in their structure interact with negatively charged groups on the polymers, thus leading to complex formation. Barkhordari et al. (2014) prepared carboxymethylcellulose/DLH composite hydrogels by heating the alkaline solution of the two components; the high pH promoted the deprotonation of the carboxyl groups so it was possible for the multivalent metal ions to interact with them. The cationic layer can also bind other anions; thus, they also show potential as adsorbents (see Sect. 7.2). The cations present in the structure also affect the gel properties: Yadollahi et al. (2015c) compared different carboxymethylcellulose/DLH composites, and they found that DLH containing zinc or copper cations also provided antibacterial activity to the gels.

6.3.2 Metal Nanoparticles

The preparation of gels containing metal particles has two major requirements: the nanoparticles need to be homogeneously dispersed in the gel structure and interactions with the polymer should prevent their diffusion into the environment. They are usually added in salt form to the polymer gel: as they are present as ions due to the dissociation, charged groups on the polymer chain can bind them to the gel network. In earlier studies, copolymers with synthetic polymers were used, but recently the nanoparticles were also incorporated in a wide array of pure polysaccharide hydrogels: systems based on cellulose derivatives (Hebeish et al. 2013), starch (Villanueva et al. 2016), chitin and chitosan (Kumar et al. 2012, 2013), alginate (Obradovic et al. 2012), and even dextran (Ma et al. 2009). The synthesis heavily depends on the metal type. Silver is a very popular choice for antibacterial nanoparticles; it is added to the gel as aqueous solution of AgNO_3 . There are two available methods: either the crosslinked gel is immersed in the silver nitrate solution (Ma et al. 2009), or the salt is added to the dissolved polymer before the crosslinking (Yadollahi et al. 2015a); this ensures the homogeneous dispersion

of the nanoparticle. The next step is the reduction of the silver cations, leading to the formation of silver particles. Antibacterial hydrogels containing gold nanoparticles were also synthesized. Marsich et al. (2011) used HAuCl_4 precursor to prepare modified chitosan/alginate/gold hydrogels.

While the effect of the silver and gold nanoparticles is widely studied, their high cost is a relatively big disadvantage, leading to the investigation of the applicability of cheaper alternatives. Various metal oxides with antibacterial properties like the copper (Yadollahi et al. 2015b) and zinc (Kumar et al. 2012) oxides proved to be perfect candidates. Similarly to the silver, they are added in salt precursor form (CuCl_2 , $\text{Zn}(\text{NO}_3)_2$, or zinc acetate); the synthesis is analogous to the silver nanocomposite gels: the hydrogels are immersed in their solution and oxides are formed during an oxidation step. Metal oxide nanoparticles exhibit very good antibacterial properties despite their significantly lower cost; thus, their importance shows a constant growth. Titan dioxide is another interesting nanoparticle as it not only exhibits antibacterial activity but also improves the mechanical strength of the hydrogel (Archana et al. 2013). Unlike other oxides, it is mixed with the polysaccharide solution in its oxide form instead of using precursors.

Another interesting application is the preparation of hydrogels with magnetic properties. This is especially advantageous in the utilization as adsorbents, where the hydrogel is used in form of small beads or particles. Incorporating the magnetic particles allows the removal of these beads from the water by a magnetic field, making their recovery a lot easier. The polysaccharide also plays a major role in the synthesis: the polymer forms a coating around the nanoparticles, preventing their aggregation. Magnetic properties were first achieved by Fe_2O_3 (Kroll et al. 1996); however, in more recent experiments Fe_3O_4 nanoparticles are used as magnetic nanoparticles (Shen et al. 2011).

7 Application of Polysaccharide-Based Hydrogels

While there is a vast literature available about the potential application of hydrogels, studies related to polysaccharide-based gels are much more limited and focused on certain fields. The largest interest toward their use is in the medical field due to the biocompatibility and the common responsive behavior. The absorption and desorption of various chemicals are also utilized in the water treatment and agricultural applications—the good biodegradability is another important advantage in the latter field. Studies related to applications in other fields are so far pretty limited; thus, only a short summary is given for them.

7.1 Medical Applications

Studies focus mainly on three major applications: controlled drug delivery systems, wound dressings, and scaffolds for tissue engineering. However, to a lesser extent,

the utility of carbohydrate-based systems was investigated for the use as bulking agents and components for contact lenses, as well. Moreover, it is important to note that these applications are not strictly separate: for example, wound dressings and scaffolds often contain bioactive agents; thus, such systems function as drug delivery systems, as well.

7.1.1 Drug Delivery

The most significant medical application of hydrogels is in the field of drug delivery. Hydrogels allow the controlled release of the bioactive molecules over an extended period of time, leading to constant drug concentration in the environment and a long-term effect. The properties of the loaded molecule also play a crucial part as it determines the possible routes for their incorporation and release (Hoare and Kohane 2008). While the diffusion of small molecules occurs easily, the process is hindered by the gel network at larger molecular size. However, the swelling of the hydrogel leads to an expanded polymer network, allowing the release of larger molecules, as well. Covalent binding to the polymer backbone or the use of polymers which interact with the molecules (e.g., through ionic interactions) are also common to control the process: in this case, the interactions between the polymer and the loaded molecule need to be disrupted.

Stimuli-responsive polymers are especially favored in this field, as the dependence of the swelling behavior on the environmental properties offers another way to control the release (Qiu and Park 2001). The abundance of polyelectrolytes and polymers with thermogelling properties among polysaccharides is also a major reason for the large interest in their application (George and Abraham 2006). While gels may show sensitivity to various properties of the environment, for carbohydrate-based hydrogels, only the pH and thermal sensitivity are generally studied. The presence of charged groups leads to sensitivity to the pH due to the protonation or deprotonation. This not only affects the gel expansion, but it can also disrupt the ionic interaction with the loaded molecules. This property is crucial as it allows a convenient route for the delivery of orally administered drugs due to the varying pH in the digestive system; however, it also plays an important role in other internal applications. While a lot of polysaccharides show pH-responsive behavior, chitosan is the only common cationic representative among them, thus exhibiting significantly different responsivity. On the other hand, polysaccharides with anionic (especially carboxyl) groups are relatively common, especially due to the widely used carboxymethylation of nonionic polymers. This led a large interest toward the chitosan as it can be utilized in a different environment than the anionic polysaccharides (Bhattarai et al. 2010). However, other considerations also need to be taken during the hydrogel formation. While the destruction of the gel network often also plays a part in the controlled delivery, usually this process should be avoided as it may lead to the rapid release of the drug. For example, carboxymethylcellulose hydrogels crosslinked with Fe^{3+} are unstable in acidic environment, but the introduction of alginate copolymer improves the gel stability (Kim et al. 2012).

Thermal sensitivity is another important factor. Several polysaccharides also exhibit thermogelling behavior. If the sol-gel transition occurs under the body temperature, it allows the preparation of solutions gelling only after being injected into the body; thus, implantation is achieved without surgery. Multiple polysaccharide-based systems show thermogelling behavior at low temperatures, such as the chitosan/ β -glycerol phosphate solutions (Chenite et al. 2001). The phosphate additive not only makes the chitosan solution thermogellable, but its concentration offers an easy way to control the gel temperature. The temperature also affects the drug release in such systems, a property which needs to be taken into account, as well (Amin et al. 2012).

The preparation of injectable hydrogels does not necessarily need thermogelling behavior: photocrosslinkable systems (usually prepared through methacrylation) allow in vivo gelation through UV irradiation (Jameela et al. 2002). However, such systems are usually utilized for tissue engineering rather than as pure drug delivery systems.

7.1.2 Wound Dressing

Another major application of the hydrogels is the wound dressing. The function of the dressings is not only to prevent the infection but also promote the healing process. Moreover, several factors can hinder the healing—for such healing-impaired wounds, further considerations are required in the dressing preparation. Hydrogels are only one of the numerous types of dressings, but their properties such as the high water content or the ability to absorb wound fluids make them preferable compared to other products (Stashak et al. 2004). This not only provides a cooling effect for the damaged skin, but the moist environment is also beneficial during the healing process. Physically crosslinked alginate dressings are especially important polysaccharide-based systems; such products are widely available even in commercial use (Boateng et al. 2008). However, they are mostly used in non-gel form like fibers. Moreover, recently adverse effects were also reported during their application due to the high Ca^{2+} concentration in the product (Ng and Cheng 2007).

Chitosan and other chitin derivatives are subjects of intense research as materials for hydrogel dressings. The degradation during their use leads to the release of various glucosamine monomer and oligomer molecules which accelerate the healing processes (Muzzarelli 1993). The healing is even faster if tissue culture medium is incorporated in the hydrogel (Kiyozumi et al. 2006). Due to these degradation products, they are also often added to other dressing systems such as alginate fibers (Knill et al. 2004) or grafted polypropylene fabrics (Yang and Lin 2004) to enhance their beneficial effect. Pure chitosan systems are mostly utilized for the preparation of photocrosslinkable hydrogels; this method offers a noninvasive way to protect the wound: the chitosan is chemically modified and after the injection onto the surface it is gelled by UV irradiation (Ishihara et al. 2001; Lu et al. 2010).

While the utilization of hyaluronic acid was in-depth investigated (Price et al. 2005), it is rarely used in hydrogel form. Cellulose-based gels also hold little importance in this application, although there are recent investigations concerning the use of hydrogels of poly(vinyl alcohol) combined with cellulose (Gonzalez et al. 2014) or its acetate derivative (Abd El-Mohdy 2013).

Hydrogels in this field often contain other components which further enhance their positive effects. Additives exhibiting antibacterial activity are especially common as the disinfection of the wound also accelerates the healing. Such effect is easily achieved by the incorporation of various antibiotics, where controlled release ensures its long-term effect. Usually, chitosan-based hydrogels are used for such systems (partly due to the antibacterial activity of native chitosan), although hydrogels based on other carbohydrates like alginate were also investigated to a lesser extent. A wide array of drugs like ciprofloxacin lactate (Yu et al. 2006) sulfadiazine (Mi et al. 2002), nitrofurazone (Kim et al. 2008b), and minocycline (Sung et al. 2010) were used as model molecules. However, there are major efforts to avoid the use of such drugs. Honey is a natural material very effective to help the healing process; it was used as a bioactive component in chitosan/gelatin hydrogels (Wang et al. 2012). Chitosan/fucoidan (sulfated polysaccharide extracted from algae) hydrogels similarly showed superior properties compared to pure chitosan (Sezer et al. 2008).

Various metal nanoparticles also exhibit antimicrobial behavior; thus, such dressings are capable to disinfect the wound. In hydrogels, the nanoparticles are dispersed in the polymer matrix (see 5.6.3.2). Silver nanoparticles are widely known for their antibacterial activity. While there is a large interest in chitosan-based composites (Lu et al. 2008), this property is also useful for polysaccharides which do not exhibit antibacterial activity like cellulose (Maneerung et al. 2008). Madhumathi et al. (2010) also observed faster blood clotting when chitin/silver nanoparticle hydrogel was applied to the wound. However, due to the relatively high cost, cheaper alternatives like metal oxides were also investigated. Archana et al. (2013) utilized TiO₂ nanoparticles to enhance the properties of chitosan–PVP gels as they show minimal cytotoxicity compared to other nanoparticles. Similar results were observed when ZnO was dispersed in chitosan hydrogel (Kumar et al. 2012).

7.1.3 Tissue Engineering

Tissue engineering is a rapidly developing medical field due to growing demand toward organs and tissues, while there is a lack of donors for transplantation. The use of polymer scaffolds for the growth of new tissues offers an alternative route to meet the demand. Hydrogels can fulfill multiple functions as scaffolds, like bulking agents providing structural integrity, but their use for the cell delivery and local controlled release of various drugs is also very important (Drury and Mooney 2003). There are several crucial requirements toward hydrogels in this field, such as good mechanical properties or porosity to allow the three-dimensional growth of the tissue. Biodegradability is another advantageous property of the

polysaccharide-based systems: the enzymatic degradation of the polymer allows the development of the tissue from the encapsulated cells (Nicodemus and Bryant 2008). There is also a large interest toward injectable hydrogels (Kretlow et al. 2007) as they allow a minimally invasive way to deliver the polymer system into the body where the gelation occurs. However, it is also important to take into consideration that *in vivo* and *in vitro* effects of hydrogel scaffolds are different (Yang et al. 2009). There are several routes available for *in vivo* gelation: the use of systems containing reactive components with a well-defined gelation time, photoinitiated crosslinking by UV irradiation (e.g., methacrylated hyaluronic acid), thermal gelation (systems capable of gel formation at body temperature such as chitosan/ β -glycerophosphate-based hydrogels), or ionic crosslinking (most notably alginate-based scaffolds). Another advantage of this method is that the polymer fills the available space; thus, no shaping is required. The delivery of various molecules such as DNA or growth factors can be used to promote the growth of the cells (Chung and Park 2007); these systems proved to be much more effective than agent-free polymer scaffolds (Kolambkai et al. 2011) or individual injection of the bioactive agents (Simmons et al. 2004) due to the slow release. *In vitro* preparation also has its advantages: such 3D scaffolds are suitable for evaluating the effect of new bioactive molecules on the target cells as they provide more precise information than 2D models (Gurski et al. 2009).

The application requirements vary heavily as specific considerations are required depending on the cell type (Kim et al. 2011). Therefore, the literature regarding the application of polysaccharide-based hydrogels in this field is very diverse. There is also a huge variety of the hydrogel systems utilized: such studies rarely involve pure polysaccharide hydrogels with the exception of bacterial cellulose, instead they are used as a component for various copolymers, blends, and composites formed with other polysaccharides, polypeptides, synthetic polymers, or even minerals (Van Vlierberghe et al. 2011). The most important representatives are chitosan (Kim et al. 2008a) and hyaluronic acid (Collins and Birkinshaw 2013), but cellulose (Svensson et al. 2005) and alginate (Venkatesan et al. 2015) show a large potential, as well. As it was mentioned previously, the literature shows large diversity based on the targeted tissue; however, the cartilage (Svensson et al. 2005; Muzzarelli et al. 2012), bone (Venkatesan et al. 2015; LogithKumar et al. 2016), and skin (Fu et al. 2013) tissue engineering is an outstanding field for the application of polysaccharide hydrogels. The number of polysaccharides investigated for the sole delivery of various bioactive molecules is much smaller compared to the preparation of scaffolds for cell delivery: studies focus mostly on hydrogel systems based on hyaluronic acid (Segura et al. 2005a; Ekaputra et al. 2011; Lei et al. 2011) and alginate (Simmons et al. 2004; Krebs et al. 2010; Jeon et al. 2011).

7.1.4 Bulking Agents

An interesting application of hydrogels is their utilization as space-filling materials. Their role in the tissue engineering as bulking agents was previously discussed;

however, their medical utility is not solely limited to this field as they show a large potential in the urology, as well. Urinary incontinence is a common disorder for women and injectable hydrogels allow a minimally invasive way for its treatment. Currently, only hyaluronic acid-based bulking agents are available in the commercial use as polysaccharide-based products (Vaizey and Kamm 2005; Mohr et al. 2013). However, Thornton et al. (2004) also investigated the application of various alginate hydrogels. They noted that covalently crosslinked alginate shows good potential for such use, although very high crosslink density increases the inflammatory response.

There are some advances toward their use in the dietary applications, as well. Such products are utilized to promote the weight loss as an alternative for more drastic strategies like surgery. Hydrogels offer a novel way to achieve such effect compared to the currently available products due to their very high water absorbing capacity. Sannino et al. (2006, 2010) investigated the use of carboxymethylcellulose/hydroxyethylcellulose hydrogels as stomach bulking agents: the copolymer not only showed high water uptake at acidic pH, but the results of tests regarding biocompatibility were also favorable. Another interesting approach for the hydrogel utilization is the preparation of oil bulking agents: by incorporating oil droplets in the gel structure, such systems can serve as replacement for animal fat (Ruiz-Capillas et al. 2013; Herrero et al. 2014).

7.1.5 Contact Lenses

The preparation of contact lenses is another field where the properties of the hydrogels excel. However, studies related to the preparation of polysaccharide-based contact lenses are much more limited. While contact lenses based on chitosan/gelatin composites were successfully synthesized and the products showed good properties (Shi and Tan 2004), no further advancement toward their commercial use was made. On the other hand, the incorporation of non-crosslinked hydrophilic polysaccharides such as hyaluronic acid (Ali and Byrne 2009) and hydroxypropylmethylcellulose (White et al. 2011) in contact lens offers a way to reduce ocular dryness caused by the lenses and reduced protein sorption through their slow release, effectively functioning as a wetting agent on the lens surface. A more long-term effect can be achieved by photocrosslinked hyaluronic acid, where the properties are also affected by the crosslink density (Weeks et al. 2012). Moreover, polysaccharide coatings even allow the incorporation of bioactive molecules to prepare lenses capable of controlled drug delivery (Hu et al. 2014).

7.2 Water Treatment

Wastewater usually contains a large amount of contaminants which are often harmful to the health; thus, they need to be removed from the water. There are

several different methods available, for example, the precipitation of pollutants or the application of adsorbents. In the latter method, hydrogels with superabsorbent properties show a large potential due to their excellent swelling properties, which helps the removal of the contaminants. This requires interaction between the pendant groups on the polymer and the pollutant so that the molecules do not leave with the water from the gel matrix during the immersion. The adsorption can be achieved even by weak interactions, like hydrogen bonds or hydrophobic interactions. However, in presence of charged (usually carboxyl) groups on the polymer backbone, strong ionic interactions can form with pollutant if the latter is also present in dissociated form, leading to significantly better adsorption. In this case, the sorption occurs either by ion exchange with the counterions of the charged groups or by complex formation (Veglio and Beolchini 1997). Charged groups can also be introduced to the gel by various copolymers; thus, the application of a wide variety of the polysaccharide-based gels was investigated. Studies focus mostly on the adsorption of the positively charged pollutants; chitosan-based gels were used for the removal of anionic contaminants, as well.

Heavy metals form one of the most important pollutant groups as industrial wastewater is often contaminated by them. A lot of them are highly toxic even in very low concentration; thus, their removal during the water treatment is crucial (Sud et al. 2008). As the metal ions are positively charged, the polymer must have negatively charged pendant groups to bind the metal ions. The use of Ca-alginate complexes was intensively studied. On the one hand, the pollutants disrupt the ionically crosslinked network; thus, the cations used for the gelation are released to the environment. However, if the alginate complexes are protonated via acid treatment, the metal ions are bound through the ion exchange with the protons, while the egg-box structure formed by the crosslinker ions is not affected by the change in the environment (Ibáñez and Umetsu 2002). The mechanical stability of the gels is also crucial: Wang et al. (2013a) significantly improved the mechanical properties of alginate beads by SiO₂ doping with minimal change in the adsorption capacity. The alginate complexes showed good efficiency for adsorbing several heavy metals like Cr³⁺ or Cd²⁺ from polluted water (Ibáñez and Umetsu 2002, 2004; Papageorgiou et al. 2006). Moreover, studies of the interaction with multi-valent ions (Menakbi et al. 2016) indicate that they are capable of binding other common metal ion contaminants, as well.

Another interesting method is the synthesis of magnetic hydrogels. In this case, various magnetic particles like Fe₃O₄ are coated with the polysaccharide hydrogel, leading to the formation of very small gel particles (Liu et al. 2012) which are easily removed from the treated water by a strong magnetic field.

Dyes are also common pollutants of the wastewater, especially in the textile industry. While not as toxic as heavy metal, several dyes are regarded as hazardous materials due to their health risk. The chemical structure of the dye is a key factor which determines the possible binding mechanism. The application of hydrogel adsorbents for dye adsorption was investigated only for dyes with charged groups. While the interaction of hydroxyl and other groups with the dye molecule also leads

to the adsorption of the pollutant, excellent adsorption can be only achieved when charged groups capable of ionic interactions are present.

For pure polysaccharide hydrogels, the adsorption of anionic dyes was mainly investigated. For this application, chitosan-based hydrogels show a large potential. The amine groups at low pH become protonated; thus, they form ionic bonds with the anionic dye. Opposed to the adsorbents used for cationic dyes, chitosan-based gels show the highest adsorption at acidic pH. Increasing pH leads to the deprotonation of amine groups and the dye is bound only with weak interactions, resulting in a significantly lower adsorption capacity. The adsorption capacity can be further enhanced by additives like surfactants (Chatterjee et al. 2009). Shen et al. (2000) also compared chitosan with chitosan-Fe(III) hydrogels prepared from FeCl_3 solution. The Fe(III) groups can also interact with the dye molecules, improving their sorption. By introducing Fe_3O_4 nanoparticles, the chitosan-Fe(III) complex also exhibited magnetic properties. Cationic hydrogels can be prepared from other polysaccharides, as well. Yan et al. (2009) synthesized hydroxypropylcellulose gels by crosslinking the polymer with epichlorohydrin and ammonia at alkaline pH. The amino groups in the crosslinks led to a high adsorption capacity toward anionic dyes.

Studies related to the removal of cationic dyes are more limited. While alginate hydrogels showed good potential in this field (Aravindhan et al. 2007), most studies investigated the use copolymer systems formed with acrylates (Cai et al. 2013; Zhang et al. 2014a). Composite gels with a mineral component are also commonly used for this application. The cationic dyes interact with the anionic clay through the exchange of cations surrounding the surface (Wang et al. 2004a).

Polymers with charged groups were also utilized for other pollutants. Methylcellulose/acrylamide hydrogels proved to be successful in adsorbing paraquat pesticide from water (Aouada et al. 2009). Chatterjee and Woo (2009) used chitosan hydrogels for the removal of nitrate as an alternative method for denitrification. However, the efficiency of the adsorption heavily depends on the pollutant, as well. Sowyma and Meenakshi (2013) investigated the effect of various ionic molecules on the adsorption: different ions showed different affinity toward the hydrogels; thus, the hydrogels show a degree of selectivity toward certain pollutants. This is advantageous as lower adsorption capacity is required for the removal of target pollutants during water treatment.

7.3 Agricultural Applications

Agricultural applications of superabsorbents also show a large potential. In the present, most commercially available products are acrylate-based superabsorbents; thus, agricultural studies mostly focus on their utilization, as well. However, recently there is a growing interest toward the application of renewable resources as a greener alternative. A major advantage of the carbohydrate-based superabsorbents is the excellent biodegradability in soil. Studies related to the agricultural use can be

separated into two categories: delivery of chemicals and soil conditioning. As the cost efficiency is a major factor due to the volume of the hydrogels required for the modification of the soil, only the most abundant polysaccharides are of large interest.

7.3.1 Fertilizer Release

The delivery of various compounds into the soil in a controlled manner is an application analogous with the drug delivery in pharmacy: the gel allows the slow release of the chemicals; thus, they exhibit their beneficial effect over a long period of time. As the bioactive agent is enclosed in the polymer matrix, the gel network needs to expand to allow the release of the incorporated molecule. While in the drug delivery can be controlled by a wide array of environmental parameters such as the pH or temperature, in the agriculture the gel expansion is controlled by the presence of moisture, leading to the swelling of the hydrogel, as other properties show a large variance between the soil types. The incorporated molecule can have multiple functions: the addition of fertilizers improves the plant growth, while other agents like pesticides and fungicides offer pest control. Such applications were widely studied with acrylate-based gels (Rudzinski et al. 2002); investigations related to the polysaccharide-based ones are more limited and even then, such systems are mainly copolymers formed with synthetic polymers. Characteristically acrylates are added as copolymers, most notable being the acrylic acid and acrylamide. However, other hydrophilic polymers such as the PVA (Han et al. 2009; Jamnongkan and Kaewpirom 2010; Li et al. 2015) are also relatively frequent components.

Urea, a common nitrogen fertilizer is the most common model molecule for the investigation of desorption kinetics, although the release of other components like phosphates was also studied (Rashidzadeh and Olad 2014). There are two major methods for the incorporation of the fertilizer: either the bioactive agent is added as a powder during the gel synthesis, or the crosslinked sample is immersed in its solution to allow the sorption. In the latter case, composites containing clay minerals are common, as the inorganic component improves the sorption of the organic molecule (Bortolin et al. 2013). Moreover, the interaction also leads to slower release compared to pure hydrogels (Rashidzadeh et al. 2014). For the production of fertilizers, copolymers of alginate (Abd El-Rehim 2006; Wang et al. 2013e) and chitosan (Jamnongkan and Kaewpirom 2010) are of major interest due to their advantageous properties. These polymers not only offer good biodegradability, but degradation products like oligo-alginates also promote the plant growth (González et al. 2012). A novel method for the preparation of chitosan-based nanoparticle fertilizers was also created, where the particles were formed with an inner chitosan and an outer acrylate coating (Wu and Liu 2008; Corradini et al. 2010). The application of starch (Guo et al. 2005; Han et al. 2009) and cellulose-based copolymers (Bortolin et al. 2012, 2013; Li et al. 2015) was also investigated due to their lower cost. Sulfonated starch/PAA hydrogels were used to prepare a phosphate fertilizer from phosphate rock, a normally difficult-to-utilize phosphorus source

(Zhong et al. 2013). Recently, pure polysaccharide-based gels were also investigated for slow fertilizer delivery. Both ionically (Davidson et al. 2013) and chemically (Ni et al. 2011) crosslinked cellulose derivative superabsorbents proved to be a viable alternative for the copolymer-based fertilizers. Interestingly, chemical cellulose acetate hydrogels crosslinked with polycarboxylic acid were also studied besides the usual cellulose ethers (Senna et al. 2015).

7.3.2 Pest Control

While the focus of the studies is on the application as fertilizers, hydrogels also allow the controlled release of other chemicals, which offer protection against pests (pesticide), weeds (herbicide), and fungi (fungicide). The largest interest is shown toward the controlled release of pesticides. The incorporation of the molecules is similar to the method detailed for fertilizers. A wide array of pesticides were examined in such experiments, and the release kinetics was also determined. This is important because the chemical structure of the bioactive agents also affects the release kinetics (Abd El-Mohdy et al. 2011). First, such experiments were carried out with starch matrices crosslinked with formaldehyde (Kulkarni et al. 1999; Kumbar et al. 2001), but later the interest shifted toward alginate-based systems. Both ionically and chemically crosslinked alginate system showed good potential for the incorporation. While Ca^{2+} cations are the standard crosslinkers of the physical gels (Roy et al. 2009). Işıklan (2007) observed that by using different multivalent cations, the release kinetics is controllable. Chemical crosslinking with glutaraldehyde was utilized for blends with other polysaccharides and polypeptides (Kulkarni et al. 2001; Işıklan 2006). Chitosan-based controlled release systems were also prepared: while Rao et al. (2006) used AAm-g-PVA IPN structured gels, Yi et al. (2011) avoided the use of crosslinkers and copolymers by using azide functionalized photocrosslinkable chitosan.

Herbicides were investigated to a smaller extent, despite their encapsulation in starch already being studied decades ago (Trimmell et al. 1985). Cellulose derivative-based gels show a large potential in this field. In earlier experiments, the copolymers of hydroxyethylcellulose were used (Rehab et al. 1991), but recently the carboxymethylcellulose/clay gels became more important: the easy ionic crosslinking through the carboxyl groups renders the copolymers redundant (Li et al. 2008, 2009). The presence of clay not only slows the release of the agent, but its rate can be adjusted by the clay type and ratio. The encapsulation also leads to lower environmental impact: Grillo et al. (2014) observed that herbicide in chitosan gels showed lower toxicity despite its activity being not affected.

Studies related to the controlled release of fungicides are few. Singh et al. (2007, 2009a, b) investigated the application of various starch gels in this field. While copolymers with acrylates were also prepared, the addition of ionically crosslinked alginate proved to be a good alternative for the synthetic polymer component. Experiments were carried out with thiram as a model fungicide; the release rate was controlled by the crosslink density.

7.3.3 Soil Conditioning

Another application field with a growing significance is the soil conditioning: the goal is to improve the water retention of the soil, thus increasing the yield of the agricultural plants and lowering the need of the irrigation. Moreover, such modification may allow cultivation even in lands with very poor retention such as sandy soil. Superabsorbents are capable of trapping large amounts of water, thus decreasing the gravitational drain of free water after the irrigation. However, the water is not strongly bound in the gel structure; thus, it is available for the plants. As gels with superabsorbent properties are used usually for the controlled release of bioactive agents, a large part of the related studies also investigated the effect of the gels on the water retention and plant growth. Similarly, the majority of such experiments used polysaccharide/acrylate systems as model superabsorbents. Acrylamide is an especially popular co-monomer which was used for copolymerization with carboxymethylcellulose (Ibrahim et al. 2007), starch (Qiao et al. 2016) and alginate (Abd El-Rehim 2006). The application of pure polysaccharide superabsorbents was also studied. Nnadi and Brave (2011) prepared carboxymethylcellulose/starch gels by pregelatinization and ionic crosslinking. The superabsorbent mixed into the soil in 0.3–0.6% concentration significantly promoted the plant growth. Biodegradability is also a crucial factor in this field. Superabsorbent gels from succinic acid-crosslinked starch (Yoshimura et al. 2006) showed similar or only slightly slower biodegradability than pure starch depending on the synthesis conditions. Alginate and chitosan hydrogels are also very good candidates for this application: as mentioned previously, the products of the hydrogel degradation promote the plant growth, leading to more desirable properties (Abd El-Rehim 2006). In the future, chitosan-based gels might also have a larger role, as they show fungicidal activity (Badawy et al. 2004).

7.4 Other Applications

The potential application of hydrogels is much wider than the fields covered so far in this section. However, there are only a few studies related to these uses concerning polysaccharide-based hydrogels. For example, while the application of polysaccharides in catalysis was investigated, especially in case of chitosan (Guibal 2005), they are not utilized in hydrogel form. In the few available studies, the polysaccharide hydrogels are used as a matrix for the immobilization of the nanoparticle catalyst (Saha et al. 2010; Wu et al. 2012b). In some cases, the hydrogel itself catalyzes the reaction: Reddy et al. (2006) used chitosan gel as a catalyst for aldol and Knoevenagel reactions. In sensors, the hydrogel functions as the structural component; glucose (Brown et al. 2005), phenol (Zhang and Ji 2010), and enzyme-sensing (Ebrahimi and Schonherr 2014) systems were prepared from chitosan-based hydrogels. Another interesting utility is the synthesis of self-healing gels. In such systems, defects and cracks can heal over time; thus, the structural

integrity is maintained—this is very advantageous in numerous applications to improve the performance of the material (Thakur and Kessler 2015). Although there is little literature available for polysaccharide-based self-healing hydrogels, recently there is a rapidly growing interest in their utilization as multiple polysaccharides like alginate (Miao et al. 2015; Pettignano et al. 2017), cellulose (Zheng et al. 2015; Liu et al. 2016) and chitosan derivatives (Wei et al. 2015) proved to be capable to form such systems.

8 Conclusions

The application of polysaccharides for hydrogel formation has a bright future. They are not only cheap and abundant materials, but a wide array of methods are available for the gel formation. The large variety in the functional groups results in properties advantageous in several applications, such as the responsive behavior. Moreover, the easy chemical modification and mixing with other natural polymers allow a convenient way to achieve the desired properties. Such systems offer a more environmentally friendly and sustainable alternative for the acrylate-based products. Currently, the main interest lies in copolymers and blends with synthetic polymers; thus, the advantages of both components can be utilized simultaneously. However, the trend is shifting toward pure polysaccharide and other natural polymer-based systems as they proved to be a good substitute for acrylates in an increasing number of fields.

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