General Introduction

Highlights

This chapter provides a precise description on the development of bio-based hydrogels, the utilization of polysaccharide as a renewable feedstock for them, the importance of their building blocks; and different modification techniques used to develop hydrogels. This chapter also includes a concise account on the different spectroscopic, microscopic, and analytical techniques employed to characterize hydrogels. Further, the various properties of hydrogels also are discussed thoroughly. A comprehensive discussion on the applications of hydrogels in various domains is also presented to evaluate the importance of these materials. Further, the chapter elucidated the scopes of hydrogels in the immersing fields. Lastly, the chapter mentioned the objectives for the present investigation and the plan to execute the research work.

Parts of this chapter is published as a chapter in an edited book

[1] Sarmah, D., Bora, A., and Karak, N. Hydrogel Nanocomposites Derived from Renewable Resources. In Pathania, D. and Singh, L., editors, *Bio renewable nanocomposite materials: For electrocatalyst, energy storage, and wastewater remediation*, Pages 269-285. American Chemical Society, 2022.

1.1. Introduction

Polymeric materials have been playing an indispensable role in the modern society, transcending ancient times to the modern age as of now [1]. The development of various polymers with aristocratic properties and their uses for multipurpose applications has drawn remarkable research interest both in industry and academia. In the modern civilized society, life without polymeric products is almost impossible due to myriad applications in diverse fields. Most interestingly, the tailorable properties, low production and maintenance cost, easily available relativity cheap raw materials, the fields of polymeric materials have received a skyrocketing impulse over other materials. Among the various polymeric materials, "hydrogel" is one of the most attractive high performing polymeric products with extra-ordinary water absorption capacity [2,3]. The presence of huge numbers of hydrophilic groups such as carboxylic, amino, hydroxyl, amide, and sulfate renders them excellent water absorbing ability [4], with a large expansion in their network structure, which is known as "swelling". The presence of cross-linker prevents them to disintegrate during swelling, and also restricts the complete destruction of the three-dimensional network. Moreover, along with water, they are also able to absorb various physical solutions such as brine, other electrolytes, as well as many biological solutions like sweat, urine, blood, etc. [5].

Recently, these highly hydrophilic, "soft and wet" materials become one the most attractive alternatives in most of the real-life applications including agriculture [6,7], biomedical [8, 9], pollution control sector [10,11], personal hygiene applications [12], energy and energy related applications [13], etc. Thus, owing to the huge applicability, in the recent days the exploitation of hydrogels research is rapidly growing across the globe.

In the initial stage, synthetic hydrogels have received extreme importance because of high water absorption capacity, extended service life and easy process ability. But the use of these hydrogels leads to an unbearable environmental and economic loss of the society as well as forced the society for the global dependence on the petroleum-based resources [14]. Non-degradability of these synthetic monomer-based hydrogels creates some serious environmental issues including oxygen demand, septic systems, and landfills. In addition to these, petroleum-based polymers have a negative impact on the economy, since the price of these raw materials is showing an increasing trend, almost always. Thus, even though the whole world enjoys the benefits of synthetic monomer-based hydrogels, the utilization of fossil fuel-based feedstock leads to non-sustainability and serious environmental problems. The extremely growing adverse impact of petroleum-based materials on the ecosystem and the environment compels the society to an immediate replacement of these non-degradable materials with biodegradable and sustainable ones. For such switching of materials, the scientists and the industries require an innovative alternative for the production of renewable resources-based materials with the potential to meet the demands for various applications. In this vein, polysaccharides have received immense importance for production of various bio-based materials due to their extraordinary properties like excellent hydrophilicity, biocompatibility, biodegradability, and availability [2,3]. They are the materials with bio-based origin and are extracted mainly from different parts of various plants and other living organisms. They are consisting of different monosaccharides or their derivatives including D-fructose, D-galactose, D-glucose, D-xylose, L-galactose, D-mannose, and L-arabinose, etc. [15, 16]. Polysaccharides consist of only one kind of monosaccharides known as homopolysaccharide, while those constituted of more than one unit are known as heteropolysaccharides. Different polysaccharides not only differ by their nature of origin or constituents but also differ in their chain length and branching. These dissimilarities provide numerous attractive properties to these bio-derived materials that make them suitable for hydrogel preparation [16, 17]. Starch [18], cellulose [19], agar [20], chitosan [21], alginates [22], etc. are some widely used hydrophilic polysaccharides with sky-high utilization in hydrogel production. The extensive utilization of these materials is due to their tailorable properties via physical or chemical modification techniques. In addition to the highly hydrophilic properties, the production of polysaccharide based-hydrogels with smart properties like mechanical toughness, shape-memory, high stretchability, and self-healing ability can be possible through advanced modification strategies.

However, in the current scenario, the fabrication of polysaccharide-based hydrogels is not up to the mark and demands more environment friendly materials with smart attributes. In the ever-growing scientific world, there are always scopes for new achievements for better performance. Thus, the preliminary evaluation divulges the urgent requirement of smart biocompatible hydrogel with multi-functionalities and smart properties to fulfill the demands of the modern civilization for numerous applications.

In this endeavor, utilization of various polysaccharides with different monomers, cross-linkers, may direct toward a well-defined research proposition. Moreover, to overcome the recent drawbacks, modern technologies with high performing cross-linking strategies are the utmost important to provide some skyrocketing urge. Thus, the recent investigation directs towards the fabrication of polysaccharides-based hydrogel with smart attributes to achieve environment friendly sustainable materials to boost the existing hydrogel research.

1.2. Historical background

The term ‘hydrogel’ first came into sight in 1894 to describe a colloidal gel made up of inorganic salts [23,24]. However, that material was indeed not the typical cross-linked hydrogel, as found today. The first synthesis of hydrogel was in 1938 by thermal polymerization of acrylic and divinylbenzene [5,25]. In 1960 Wichterle and Lim reported a water swollen cross-linked hydrogel via free radical polymerization of 2-hydroxyethyl methacrylate (HDMA) and found substantial use as soft contact lenses [26]. This is the first report on the applications of hydrogel and introduces a new class of material for biomedical uses. However, under some reaction conditions, the hydrogel was unable to provide sufficient oxygen to the eyes, especially when the eyelids are closed and the hydrogel was also mechanically fragile [23,29]. These disadvantages sparked the research towards the improvement of the hydrogel as contact lenses by using *N*-vinylpyrrolidone with HDMA [23].

N-isopropylacrylamide has wide applicability as a synthetic monomer for hydrogel synthesis. Although poly(*N*-isopropylacrylamide) was synthesized in 1950s [28] but did not get much attention until its temperature dependent phase transition behavior is reported by Heskins and Guillet in 1968 [29]. They ascribed the lower critical solution temperature of the material. Further, *N*-isopropylacrylamide monomer was copolymerization with various other monomers and found extensive uses in various fields including biomedical and enhanced oil recovery applications [23].

In 1970s Northern Regional Research Laboratory, US produced the first commercial hydrogel from alkaline hydrolysis of starch with poly(acrylonitrile) with 400 times higher water absorption ability than its dry weight [30]. But the lack of enough gel strength and the cost are the major disadvantages for its market [6]. In 1978, the successful marketable production of hydrogel started in Japan for its use in female napkins. Subsequently, hydrogels as baby diapers were employed from 1980 in Germany and France. In 1987 Fanta et al. synthesized a starch and 2-acrylamido-2-

methylpropanesulfonic acid-based hydrogel with around 1700 g/g water absorption capacity by modifying the drying procedure of their previous work [31].

Poly(vinyl alcohol) (PVA), a linear synthetic polymer has found extensive used in the production of hydrogel. The first covalently cross-linked PVA hydrogel was synthesized using gamma or electron beam irradiation by Danno et al. [32]. Later to prepare chemically cross-linked hydrogels, various reactive groups such as isocyanates [33], glutaraldehyde [34], etc. are used to react with the hydroxyl groups of PVA. Moreover, to prepare PVA-based hydrogel click chemistry was also used in which azide and alkyne modified PVA components were cross-linked in the presence of Cu (I) catalyst.

Later, the focus of hydrogel research shifted towards the fabrication of hydrogel with the capability to respond to suitable stimuli such as temperature, pH, or presence of a specific molecule in solution, etc. [24]. Thereafter the progress on hydrogel research shifted for the devolvement of so called “smart hydrogels” with a wide spectrum of tunable properties such as mechanical self-healing ability, toughness, shape memory properties, etc. In recent years, hydrogels, based on double cross-linking strategy, have gained incredible research interest due to the ability to overcome the weakness of most of the hydrogels. In 2003, Gong et al. prepared a double-cross-linked hydrogel with high mechanical strength [35].

Thus, the prior art literature reveals that the field of hydrogel research is growing rapidly with aristocratic properties. However, it is obvious that there are always scopes for future investigation and development of materials with more advanced functionalities for versatile applications.

1.3. Classification of hydrogels

Hydrogels can be categorized into different classes, as described below.

Based on the source

Hydrogels can be divided into three categories based on of source of origin viz. natural, synthetic, and hybrid (combination of both) [36].

Based on the monomeric unit composition

Based on the monomeric units, there are three different classes hydrogel available, as narrated below.

(a) Homopolymeric hydrogels

The polymeric networks obtained from only a one kind of monomer are termed as homopolymeric hydrogels. These hydrogels process different cross-linked structures depending on monomer, cross-linker and the polymerization techniques used.

(b) Copolymeric hydrogels

Hydrogels comprised of more than one kind of monomers with at least one hydrophilic component and units are organized in a block, random, graft or alternating arrangement are termed as copolymeric hydrogels [37].

(c) Interpenetrating polymer network (IPN)-based hydrogel

The hydrogel made up of two independent cross-linked natural and/or synthetic polymeric components confined in a network form is termed as IPN hydrogel. In the time of hydrogel formation, one network is synthesized with immediate presence of the other. There is no covalent bonds exist in between them, but at the same time they cannot be separated without breaking the chemical bonds [38]. The semi-IPN composed of one non-cross-linked polymer with one cross-linked polymeric network [37].

Based on the long-range order in the structure

Based on the long-range order in the structure, hydrogels can be classified into three different classes [39].

(i) Crystalline: presence of high long-range order structure, with high degree of crystallinity

(ii) Amorphous (non-crystalline): no order or completely haphazard structure

(iii) Semicrystalline: combination of both crystalline and amorphous phases, where crystalline phase is relative less.

Based on the physical appearance

Depending on the polymerization processes employed during hydrogels formulation, they adopted difference in physical appearance such as film, lump, microsphere, etc.

Based on the charges

Based on electrical charges hydrogels can be classified into three groups. These are

(i) Neutral: No electrical charge in the structure

(ii) Ionic (including anionic or cationic): Presence of cationic or anionic charge in the structure
(iii) Amphoteric: Both cationic and anionic groups are present in the structure.

Based on the cross-linker

Hydrogels can be divided into three different classes on the basis of the cross-linked structure [40].
(i) Chemically cross-linked hydrogel: Hydrogels composed of covalently cross-linked chemical networks. They are stable and possess permanent structures.
(ii) Physically cross-linked hydrogel: Hydrogels results from various physical interactions such as hydrogen bonding, ionic interactions, with reversible structures are termed as physically cross-linked network.
(iii) Several hydrogels comprise of both chemical and physical networks and found to have extraordinary mechanical strength and termed as dual cross-linked hydrogels [41].

1.4. Materials and methods

1.4.1. Materials

By definition, hydrogels are the polymeric compound having hydrophilic properties. Thus, hydrogels are generally prepared using hydrophilic monomers. However, hydrophobic monomers are also sometimes used to regulate the properties for a specific purpose. Generally, synthetic monomers have wide applicability in hydrogel preparation due to their remarkable hydrophilicity. But, to address the ongoing issues related to the environmental degradation and sustainability of the synthetic hydrogels, various renewable resource-based hydrogels have received noticeable attention. Thus, in this context different polysaccharides have been widely used as biocompatible feedstock with remarkable hydrophilicity and biocompatibility. However, to incorporate some astonishing properties on these polysaccharides, synthetic monomers are grafted on their backbone or different cross-linkers have been used. The different building blocks, cross-linker, and initiators used for the preparation of hydrogels have been summarized in this section. Further, different preparative methods used for the preparation of hydrogels have also been demonstrated.

1.4.1.1. Polysaccharides

Polysaccharides are an important class of biopolymers containing many monosaccharide units linked through glycosidic linkages [42]. They are the most abundant biopolymers obtained from different plants, animals, microbes, and algae. Their high stability, nontoxicity, renewable nature, and intrinsic biodegradability along with inherent hydrophilic properties make them suitable candidates for hydrogel preparation. The presence of various functional groups such as –OH, –COOH, $–NH_2$, and $–OSO_3$ offers excellent tunable properties along with hydrophilicity [42]. The wide range of molecular weights and different chemical compositions also provides structural diversity and numerous properties in polysaccharides. Thus, polysaccharides-based hydrogels have received extensive attention from the researchers over the last few decades. Various polysaccharides used for the preparation of hydrogels have been discussed in this section and their general structures are shown in **Table 1.1.**

(a) Starch

Starch is one of the most abundant plant-derived polysaccharides applied for the synthesis of hydrogel [43]. It can be considered as the most prominent candidate for hydrogel preparation due to its complete biodegradability, low cost, easy availability, and noteworthy hydrophilicity. It can be extracted from different parts of various plants including roots, leaves, seeds, etc. Typically, starch is a polymeric carbohydrate consisting of two homopolymers of D-glucose; amylase and amylopectin (**Figure 1.1**). Amylose is a linear α-D (1, 4)-glucan while amylopectin is a branched polysaccharide joined together by 1, 6-glycosidic linkage [44,18]. Amylose has a tightly packed linear structure, while amylopectin is highly branched. The amount of amylose and amylopectin varies depending on the source of extraction and affect the molecular order, crystallinity, and gelatinization process of starch. About 70% starch granule is considered as amorphous and the other 30% is crystalline in nature. The crystalline region contains mainly the amylopectin part, while the amorphous region is due to the amylose content in starch [18]. The presence of secondary hydroxyl groups at C-2 and C-3 of each glucose unit, and one labile primary hydroxyl group at C-6 renders hydrophilicity and the primary hydroxyl group of starch can be easily grafted to a polymeric chain. Thus, the starch backbone could be easily utilized for hydrogel preparation with numerous properties and wide applicability.

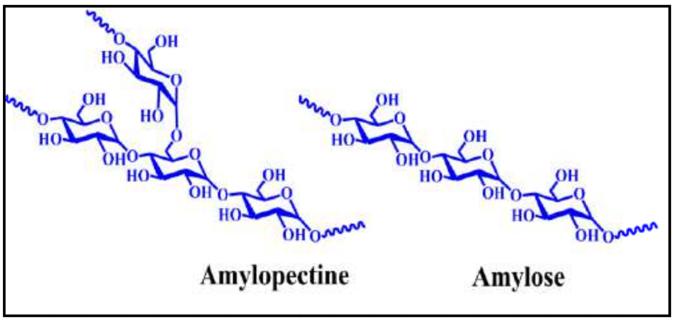


Figure 1.1. Structure of starch

Depending on the source of extraction different variations of starch exist such as corn, potato, wheat, tapioca, etc. Among this, tapioca starch is extracted from the roots of cassava plants and with c type structure [45]. Due to its high molecular weight, it is insoluble in water at room temperature and has enough labile primary hydroxyl groups in each repeating unit than the low molecular weight soluble starch. These labile primary hydroxyl groups can be easily cross-linked or can further modify by grafting hydrophobic or hydrophilic chains [46].

Due to its highly hydrophilic nature, starch can be easily hydrated and retrograde through a three-step thermal process to achieve gelatinized starch. In the first step, swelling occurs by absorbing the water used to dissolve the starch molecules. Thereafter leaching of amylose groups occur leading to gelatinization of starch and finally, retrogradation step takes place followed by restructuring and the partial recrystallization of the polymeric backbone, and the starch-based hydrogel is formed after cooling and aging. To obtain the desired property such as tunable swelling property or improved mechanical properties, grafting or physical cross-linking is done on the starch backbone. For instance, poly(dimethylsiloxane) (PDMS) was added with starch to regulate the functional and mechanical properties of the hydrogel. The physical cross-linking of PDMS provides high stretch ability suitable for flexible sensor. Besides, physical cross-linking grafting of chemically cross-linked polymeric chains was also done to enhance the swelling ability of the starch-based hydrogel. For example, acrylic acid (AA) and acrylamide (AM) grafted on the starch backbone to obtain hydrogel with outstanding swelling ability. Both physically and chemically cross-linked starch-based hydrogels achieved numerous applicability in diverse fields including wastewater treatment, biomedical applications, agricultural applications, etc. [18,47].

In addition to starch, literature advocates the worldwide utilization of various polysaccharides for hydrogel preparation. The structures of various polysaccharides and their some applications are highlighted in this section.

(b) Chitin and chitosan

Among the polysaccharides, chitin is a (β-(1→4)-N-acetyl-D-glucosamine) linkage containing natural polysaccharide (**Table 1.1**). This biopolymer is obtained from various living organisms including insects, various crustaceans such as shrimp, crab, and lobster, etc. It is also extracted from the exoskeleton of various cephalopod species such as cuttlefish, squid, and octopi, etc. [48]. Chitosan is another polysaccharide that is obtained by either chemical or enzymatic deacetylation of chitin [49]. It consists of repeating units of glucosamine and *N*-acetyl-D-glucosamine [50]. The rate of degradation and hydrophilicity of chitosan depends on the degree of deacetylation [51]. Chitosan-based hydrogels exhibit pH response swelling behavior and have wide applicability in wastewater treatment and biomedical fields.

(c) Agar

Agar is an unbranched (linear) hydrophilic polysaccharide consisting of alternating units of 3-linked-β-D galactopyranose and 4-linked 3-6-anhydro-α-L-galactopyranose (**Table 1.1**). Its molecular weight of about 1.2×10^5 and extracted from different red algae [52]. Due to its inexpensive and thermo-reversible properties and higher mechanical strength, it has been found an increasing utilization in hydrogel preparation.

(d) Cellulose and its derivatives

Cellulose is the most abundant plant-derived polysaccharide used in hydrogel preparation containing repeating D-glucose units joined together via β-1,4 glycosidic bonds [53] (**Table 1.1**). It has a linear structure and can also be obtained from bacterial sources. Along with native cellulose various derivatives such as carboxymethyl cellulose and hydroxypropyl cellulose were also used in hydrogel formation [54].

(e) Guar gum

Another plant derived polysaccharide is guar gum obtained from guar plant. It is consists of D-mannose units joined together by β-(1-4) glycoside and D-galactose units connected in an alternating way through (1-6) glycoside linkage. In the presence of water, the galactose of mannose units undergoes chain entanglement resulting in thickening and enhancement of the viscosity of the solution. Due to its unique gelling property, it has found extensive used in various fields [55].

(f) Alginate

Alginate is a negatively charged linear polysaccharide containing repeating units of 1,4-β-D-mannuronic acid and α-L-guluronic acid residues [22] (**Table 1.1)**. It can be extracted from the cell walls of brown algae. Alginate-based hydrogel is generally prepared by using divalent cross-linking and found wide applicability in biomedical field. The ionic cross-linking methods provide ionic gelation to encapsulate various biomolecules and cells, and its low cost and low toxicity make it suitable for biomedical applications [49].

(g) Hayluronic acid

Hayluronic acid has a linear structure containing alternating D-glucuronic acid and *N*-acetyl-D-glucosamine repeating units linked together via alternating β-1,4 and β-1,3 glycosidic bonds [56]. It is a naturally occurring polysaccharides found in all living organism. Its unique viscoelastic property and biocompatibility makes it suitable as a hydrogel forming material.

(h) Pullulan

Pullulan is α(1→4) and α(1→6) linkage containing polysaccharide with nine hydroxyl groups on surface [57]. It is produced by various fungus such as *Aureobasidium pullulans*, *Teloschistes flavicans*, *Rhodotorulabacarum*, etc.

(i) Dextrins

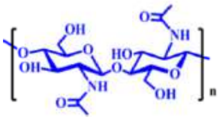
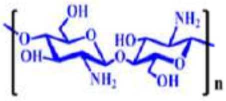
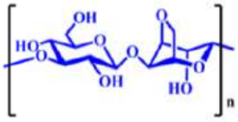
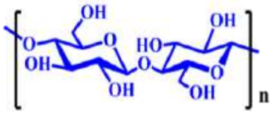
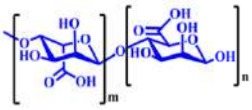
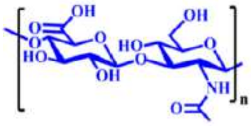
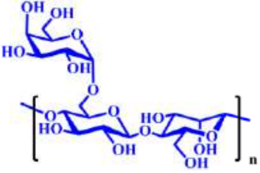
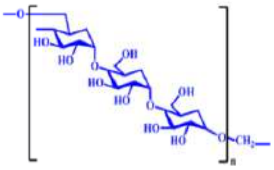
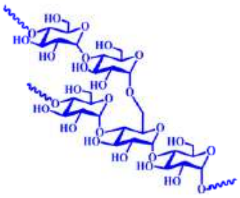
Dextrins is a low molecular weight carbohydrate obtained by the hydrolysis of glycogen and starch. Its structure consists of D-glucose units linked together by α-(1→4) or α-(1→6) glycosidic bonds and found extensive used for hydrogel preparation [58]. It is produced by acid or enzymatic hydrolysis of glyconge or starch. Its different characteristics such as gelation, hygroscopicity, ferment ability, viscosity, etc. make it suitable for preparation of hydrogel.

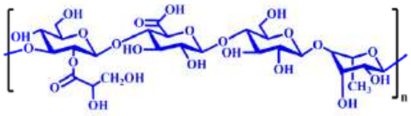
(j) Gellan gum

Gellan gum is an anionic polysaccharide with linear structure having repeating unit of α -L-rhamnose, β-D-glucose, and β-D-glucuronate with 1:2:1 molar ratio [59]. It is produced by *Sphingomonas elodea* bacteria. In native form it contains two acyl substituent, and it is removable by alkaline hydrolysis. The gel form by native form is soft and easily deformable, while the deacetylated gels are rigid and brittle.

The representative structures of some important polysaccharides that are used in hydrogel formation are given in the following table with some of their applications.

Table 1.1. Different bio-based polysaccharides with their structures and applications.

Name	**Structure**	**Application**	**Reference**
Chitin		Drug delivery and tissue engineering	[60,61]
Chitosan		Wastewater treatment, biomedical	[21,62]
Agar		Mechanically tough, self-healable material	[20,63]
Cellulose		Drug delivery, high swell able material	[19]
Alginate		Biomedical application	[22]
Hayluronic acid		Tissue engineering application	[56, 64]
Guar gum		Wastewater treatment, agricultural applications	[65, 7]
Pullulan		Tissue engineering, drug delivery applications	[57, 66]
Dextrin		Protein diffusion and release, drug delivery agent	[58,67]

Gellan gum		Tissue engineering and injectable hydrogel	[59, 68]

1.4.1.2. Hydrophilic monomers

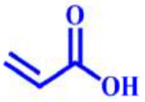
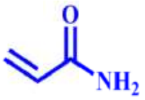
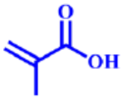
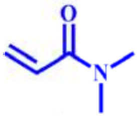
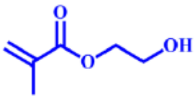
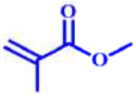
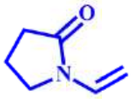
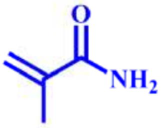
Hydrophilic synthetic monomers are more advantageous due to their highly attractive properties compared to the natural one. Synthetic monomers can produce long chain polymers with high molecular weight. However, they have poor biodegradability and biocompatibility. These two opposite facts compel the researchers to the development of hydrogel using both synthetic and bio-based components. Combination of both leads to superior swelling ability, mechanical stability, and a satisfactory biodegradability.

Among the various hydrophilic monomers AA is the simplest unsaturated monomer used for hydrogel preparation. It has one carboxylic acid group, and this group is connected to a vinyl group [69]. In the presence of a suitable cross-linker and initiator, it can undergo a free radical polymerization reaction with a highly porous (three-dimensional) 3D structure. The polymerization can be preceded both in acidic and basic medium at appropriate temperature [69]. AA-based hydrogels have the extensive swelling ability in water. Due to the presence of anionic carboxylate ions the swelling ability of the hydrogel is pH dependent and at basic pH high swelling ability is observed. This high swelling ability is due to the electrostatic repulsion of the carboxylate ions produced due to the deprotonation of the carboxylic groups [36]. AA has been huge utilization in hydrogel preparation and exploited in numerous areas extensively.

AM is one of the most frequently used neutral monomers for hydrogel synthesis. It contains one amide group connected to a vinyl double bond. Similar to AA it also undergoes free radical polymerization in the presence of cross-linker and initiator. Poly(acrylamide) (PAM) hydrogel showed extra-ordinary swelling ability which is much higher than its dry weight. The extremely large swelling ability is due to the formation of a highly porous structure after polymerization. Swollen PAM gel is soft in nature and has wide applicability in numerous fields. In addition to water, the amide group of this material has a huge affinity towards neutral or ionic species present in water, which made it suitable for various applications including a dye or metal ion adsorption from wastewater.

In addition to these, there are numerous derivatives of AA and AM along with other monomers used for hydrogel synthesis. The chemical structures and the applications of a few important synthetic monomers that are used in hydrogels are tabulated in **Table 1.2.**

Table 1.2. Different hydrophilic synthetic monomers with their structures and applications.

Name	Structure	Application	Reference
AA		Wastewater treatment, agricultural applications	[70]
AM		Agricultural applications, metal ion adsorption	[71, 72]
Methacrylic acid		Dye adsorption, drug delivery	[73, 74]
N, N-Dimethylacrylamide		Dye adsorption	[75]
2-Hydroxyethyl methacrylate		Dye adsorption	[76,77]
Methyl methacrylate		Drug delivery, mechanically tough hydrogel	[78]
N-Vinyl-2-pyrrolidone		Dye adsorption	[79]
Methacrylamide		Cancer cell culture system	[80]

1.4.1.3. Hydrophobic monomers

Along with the above hydrophilic monomers, various hydrophobic monomers are also used to synthesize hydrogels to provide some extraordinary properties such as stretchability, self-healing ability, and shape memory properties, etc. For these purposes n-dodecylmethacylate, n-hexadecyl methacrylate, stearyl methacrylate, docosyl acrylate, etc. are the most widely used hydrophobic monomers for hydrogel synthesis. The structures of these two monomers are given in **Figure 1.2** [81,82].

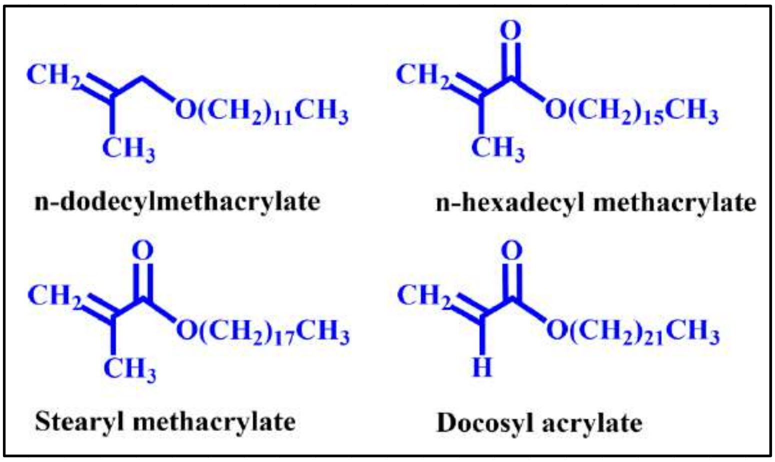


Figure 1.2. Structures of some hydrophobic monomers used for hydrogel synthesis.

1.4.1.4. Hydrophilic polymers

Sometimes instead of monomers, several hydrophilic polymers are used in the synthesis of hydrogels. They are cross-linked by using different cross-linkers or grafted to polysaccharides backbone to incorporate a wide range of functionalities into the resulting hydrogel. PVA, poly(*N*-isopropylacrylamide) (PNIPAAm), poly(ethylene glycol) (PEG), etc. are the most widely used such polymers for this purpose.

PVA is a neutral, water-soluble, synthetic polymer widely utilized for hydrogel formation. It has a relatively simple structure having a pendent hydroxyl group. The monomer of this polymer is vinyl alcohol, which is not stable in monomeric form. Thus, PVA is synthesized by hydrolysis of poly(vinyl acetate) [83]. Due to noteworthy mechanical property and hydrophilicity along with biocompatibility, PVA-based hydrogels have been found wide applicability in numerous fields including biomedical applications, [83], self-healing hydrogel [84], etc.

PNIPAAm is one of the most interesting polymers containing hydrophilic amide groups and hydrophobic propyl groups. It can undergo a lower critical solution temperature at around 34 °C. At lower temperatures, amide groups of PNIPAAm were solvated by water, while with an increase in temperature (e.g., >34 °C) physically cross-linked network formed through strengthening of the propyl groups [49].

PEG is another most common hydrophilic polymer containing hydroxyl groups in each repeating unit. It is widely used in hydrogel preparation for versatile applications, most commonly in biomedical applications [85].

1.4.1.5. Initiators

Initiators are the most important part of hydrogel preparation in the case of a radically induced polymerization process. Actually, initiation is the first step in the radical polymerization process. During this process, an active center is generated in carbon-carbon double bond. This active center than activate other monomers to propagate the chain reaction. Various initiators such as chemical initiator [86], UV [87], or redox initiators [88] are used in hydrogel preparation. There are several types of chemical initiators such as benzyol peroxide [89], potassium persulfate [90], ammonium persulphate (APS) [86], hydrogen peroxide [91], 2,2'-azobisisobutylonitrile (AIBN) [92], sodium metabisulfite [93], ceric ammonium nitrate [94], ferrous ammonium sulfate [95], etc. Along with the initiator, sometimes catalyst such as tetramethylethylenediamine is also used to accelerate the action of initiation [69]. The concentration of the initiator can influence both degree of polymerization and the properties of the hydrogel. With an increased in the concentration of the initiator, the chain length of the polymer decreases and thereby reducing the elasticity of the gel [69]. Thus, an optimum concentration of initiator is required to obtain a hydrogel with the desired quality.

1.4.1.6. Cross-linkers

Cross-linker is the most integral part of hydrogel formation. Without proper cross-linking density, hydrogels are not able to retain their integrity in the swollen state. Based on cross-linking forces hydrogels can be classified into chemically cross-linked hydrogels, physically cross-linked hydrogels, and a combination of both i.e., hybrid hydrogels [69].

Physical cross-linking are non-covalent interactions that form reversible gels. Various secondary forces exist in physically cross-linked hydrogels, the details are discussed latter section. In this section, various chemical cross-linkers used for hydrogel preparation are discussed and tabulated in **Table 1.3**.

Chemical cross-linker can be divided into two categories; the first one is used in the radical polymerization reaction. *N, N*-methylene bisacrylamide (MBA) is the most widely used cross-linker for the hydrogel preparation. It can undergo free radical polymerization reaction with acrylic and vinylic monomers in the presence of radical initiators. In free radical polymerization reaction, the cross-linker must have at least two double bonds suitable to produce free-radical [69]. The initiator changes the monomers to free radicals, which then react with other monomers to activate a chain reaction. Then the radically induced cross-linker reacts with the radicals of the polymeric chains to form a cross-linked 3D network. Very minute concentration of this cross-linker can affect the gel structure and thereby monitoring the swelling amount and mechanical toughness of the resulting hydrogel [96].

Ethylene glycol dimethacrylate is another cross-linker used in free radical polymerization reactions. It is a diester derived from ethylene glycol and methacrylic acid in 1:2 ratio. Akhtar et al. synthesized an AA and PVA-based hydrogel using this cross-linker in the presence of benzoyl peroxide as an initiator [89].

In addition to the free radial polymerization, several cross-linking agents are used in the production of hydrogel through condensation reactions or other mechanisms. Citric acid is a widely used cross-linking agents due to its hydrophilicity, non-toxicity, and low cost. It is a naturally occurring organic compound with three carboxylic groups and one hydroxyl group and can form a strong network by an esterification reaction. It helps increment in hydrophilicity of the resulting hydrogel through strong hydrogen bonding and also enhanced the thermal properties of the cross-linked gel [97].

The sodium salt of citric acid or sodium citrate is a widely used cross-linker in hydrogel preparation. It is a white powder and water-soluble compound with a sour taste [98]. It is widely used in the formation of chitosan-based hydrogel.

Another naturally occurring cross-linker is genipin, which is obtained from the gardenia fruit. It processes very much low cytotoxicity and can react with primary amines [99].

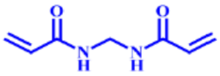
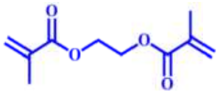
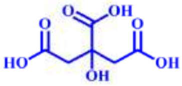
Epichlorohydrin (ECH) is another widely used cross-linking agent used to cross-link the different polysaccharides and PVA. It contains one epoxy ring, and the ring is connected to a carbon-containing to chlorine atom. In the presence of a basic environment, the epoxy ring opens leading to the cross-linking of the hydroxyl groups of the polymers. It has specific reaction conditions with an optimum amount of this cross-linker; it can offer either high swell able [100] or mechanically tough hydrogel [101]. Like ECH, ethylene glycol diglycidyl ether is another cross-linker containing epoxy ring. It has two epoxy rings located at both ends of the molecule. They are highly reactive due to the strains exist because of the presence of three-membered ring [102]. Similar to ECH, epoxy ring opening takes place during the cross-linking reactions [103].

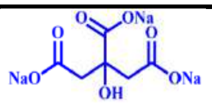
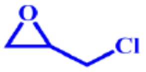
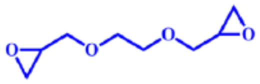
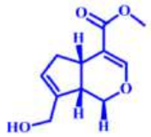
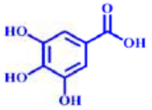
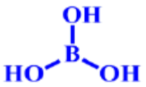
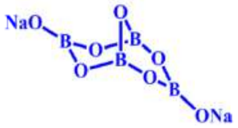
Borax (sodium tetraborate ($Na_2B_4O_7.10H_2O$)) is another widely used cross-linking agent for hydrogels. In an aqueous solution, it exists in the form of $B(OH)^{4-}$ and can react with four hydroxyl groups to form a cross-linked structure [104]. Borax cross-linked hydrogel exhibited excellent self-healing ability and swelling index with appreciable mechanical strength [105]. It is highly used to prepare polysaccharides [65] and PVA-based hydrogels. Boric acid is also used to cross-link different polysaccharides and PVA. It is a monobasic Lewis acid having the chemical formula H_3BO_3. Usually, it can cross-link 1,2- and 1,3- diols through the formation of boronate ester bond [106].

In addition to this, different cross-linker having aldehydic groups are also used to synthesize hydrogel. Glyoxal is a linear aliphatic aldehydic compound containing two aldehyde groups. It is highly reactive and has wide application as a cross-linking agent for hydrogel preparation. It can form a Schiff base with amide groups of chitosan to offer cross-linking network [107]. Another aldehydic group containing cross-linker is glutaraldehyde. It has also two reactive aldehydic groups capable of bonding with amines, phenols, hydroxyl, thiols, and imidazole groups. Due to its strong affinity for amines, it is widely used for cross-link chitosan-based hydrogels. It is one of the most efficient cross-linking agents due to the formation of a thermally and chemically more stable hydrogel. It is a cheap cross-linking agent with lower toxicity and higher reactivity [99].

Gallic acid is a trihydroxybenzoic acid and contains three hydroxy groups at 3, 4, and 5 positions. It has also been found wide applicability as a cross-linker for hydrogel preparation [108].

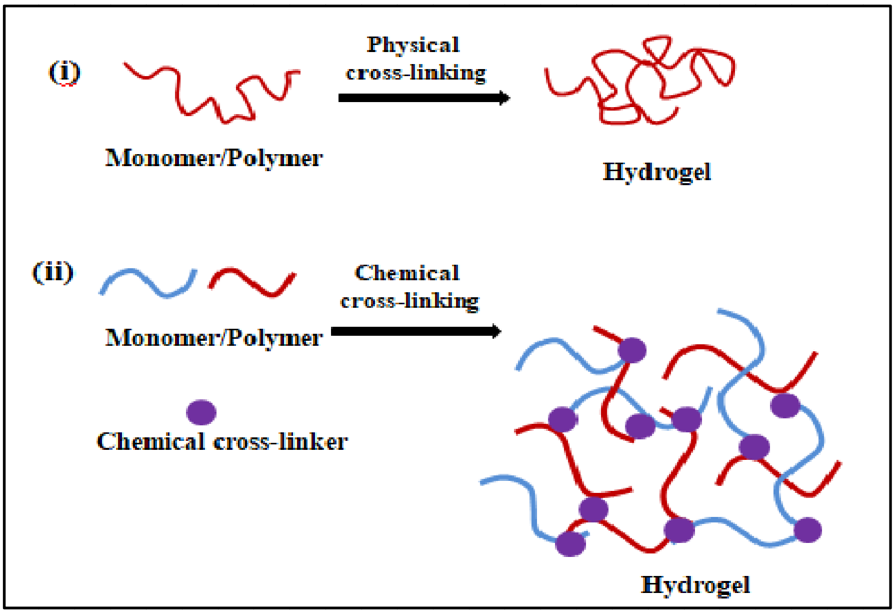
Table 1.3. Different cross-linkers with their structures and fields of applications.

Name	Structure	Application	Reference
MBA		Agricultural application, wastewater treatment	[109]
Eethylene glycol dimethacrylate		Bio medical field	[89]
Citric acid		Drug delivery	[110]

Sodium citrate		Heavy metal ion adsorption	[98]
ECH		Controlled delivery, Mechanically tough hydrogel	[100, 101]
Ethylene glycol di-glycidyl ether		Bio medical applications	[8]
Gluteraldehyde		Tissue engineering Dye adsorption	[9,111]
Genipin		Biomedical application	[112]
Gallic acid		Wound dressing applications	[108, 113]
Glyoxal		Drug delivery	[107]
Boric acid		Self-healing hydrogel	[106]
Borax		Sensing, Bio-medical applications	[104]

1.4.2. Methods

Various technologies have been implemented in the formulation of hydrogels to obtain the desired product for the targeted applications. On the whole, hydrogels are obtained from either natural or synthetic origins or a combination of both. The synthetic monomers process higher hydrophilicity than the natural ones but slower degradation rate. These two opposite properties are balanced to obtain the optimum design. Generally, there are three vital elements of hydrogel formation initiator, monomer, and cross-linker. Usually, polar monomers are used to synthesize hydrogel along with water or other diluents to regulate the heat of polymerization and the final properties. The cross-linking of the polymer chain has the major value in case of hydrogel preparation. This is done by either using chemical agents or physical cross-linking conditions, various chemical amendments, or by the introduction of radiation source [114]. The preparative methods can be classified into two broad classes, i.e., chemical and physical cross-linking methods. Chemically cross-linked methods involved the formation of new covalent bonds inside the hydrogel network, while physical interactions exist in the case of physically cross-linked hydrogels [115]. The schematic representations of both the methods are shown in **Scheme 1.1**. Both the methods can be sub-divided into several other categories as discussed later. The benefits and drawbacks associated with each of the methods are also discussed briefly to get insights into it.



Scheme 1.1. Schematic representation of cross-linking methods of hydrogel.

1.4.2.1. Physical cross-linking methods

The physical cross-linking methods of hydrogel formation involve physical interactions like hydrogen bonding, ionic interaction, hydrophobic interaction, etc. Recently, physical cross-linking can be considered as one of the most important tools due to the absence of external cross-linking agent that possesses lower toxicity that uphold the benefits compared to chemical cross-linking hydrogels. However, the hydrogels achieved through physical cross-linking methods are reversible in nature and structural imperfections or inhomogeneities may exist due to the presence of free chain ends. Moreover, the dissolution of polymer chains during the performance is one shortcoming that restricts its widespread utilization in various fields. In this section, a brief description of physical cross-linking methods is provided to understand the mechanism behind them [36].

(a) Complex coacervation (polyelectrolyte complexation)

The mixing of polyelectrolytes having cationic and anionic charges can form complex coacervate molecules. The polyelectrolytes either of natural or synthetic origin can undergo dissociation in an aqueous solution and thus phase separation occurs. The dissociated part of one polyelectrolyte reacted with the oppositely charge ion of the other polyelectrolyte resulting in a cross-linked product. Thus, the principle behind this is the phase separation of the polyelectrolytes in an aqueous solution and aggregation of oppositely charged ions from a complex structure. The electrostatic interactions between the oppositely charged ions are stronger than most of the secondary binding interactions leading to unique chemical and physical properties within the gel [48]. By using this technique, Lalevee et al. synthesize a highly stretchable hydrogel by using polycationic chitosan and polyanionic hayluronic acid [116]. The mechanical property can be regulate by varying the pH of the reaction medium and changing from fragile hydrogel to a strong stretchable hydrogel when the pH changes from the pH close to pKa of the amines of chitosan to the pH slightly inferior to the pKa of carboxylic acid groups of hayluronic acid. However, this method suffers from serious drawbacks due to difficulty in large-scale preparation [48].

(b) Ionic-cross-linking or ionic-interaction

Polysaccharides containing ionic groups such as sodium alginate can form cross-linked structure in the presence of counter ions. The cross-linking reaction occurs at ambient temperature and physiological pH conditions. However, the cross-linking reaction with $CaCl_2.2H_2O$ is hard to control to obtain a uniform gelation rate with a uniform structure [39]. To overcome this drawback, Kuo et al. used various calcium salts such as calcium carbonate ($CaCO_3$) and calcium sulfate dihydrate ($CaSO_4.2H_2O$) with D-glucono-D-lactone. This reaction condition provides uniform gel with controlled mechanical strength. The gelation rate was enhanced with an increase in the number of calcium ions and the temperature of the reaction mixture. However, a slower gelation rate generates a more uniform structure with higher mechanical strength than the faster one [117].

(c) Hydrophobic interaction

Polymers having hydrophobic domains can undergo reversible thermal gelation to form physically cross-linked structures in an aqueous atmosphere. This process is also known as “sol-gel” chemistry and occurs at elevated temperatures in the presence of an amphiphilic polymer solution. To prepare the amphiphilic material, the hydrophobic segment is coupled with a hydrophilic polymer by using a post-polymerization technique. Such amphiphilic polymers are water soluble at low temperatures and start aggregating with increasing temperature to minimize the hydrophobic surface area and thus reduce the surface contacting water molecules and enhance the solvent entropy. The gelation temperature depends on the length of the hydrophobic segment, concentration, and structure of the polymer [115]. To introduce the hydrophobicity, Tien et al. carried out the *N*-acylation of chitosan using fatty acyl chlorides to fabricate a drug delivery matrix. The hydrophobic self-assembly improved the stability of the substituted chitosan and the drug release depends on the degree of acylation and the acyl chain length [118].

(d) Freeze thawing

Freeze thawing is a promising method for hydrogel preparation due to its appreciable biocompatibility and nontoxicity [119]. Usually, this method involves the freezing of the polymeric solution at a very low temperature (–20 to –80 °C) followed by thawing at room temperature. The final property of the hydrogel obtained by this method depends on the pH of the polymeric solution, freezing time, temperature, number of thawing cycles, etc. PVA-based hydrogels have been extensively prepared by using this technique. The cross-linker, initiator-free hydrogel possesses appreciable mechanical strength along with adequate biocompatibility and non-toxicity [48]. During freezing, liquid-liquid phase separation occurs followed by the formation of ice crystals. Meanwhile, hydrogen bonding occurs between the polymer chains leading to the formation of polymer crystallites. Moreover, to form the hydrogel network, the thawing process facilitates the formation of crystalline regions. The ice crystals also act as cross-linkers and generate porous structures within the gel [119]. With increased in the amount of repeated freeze-thaw cycles, the size of the ice crystals increases [48,120]. Ricciardi et.al found that the size of PVA crystallites and the degree of crystallinity increased with an increment in the number of freezing and thawing cycles [121]. This technique is also used to prepare chitosan and PVA based hydrogel [122].

1.4.2.2. Chemical synthesis methods

Even though physical cross-linking methods enjoy the benefit of the preparation of the hydrogel without the involvement of any additional chemical cross-linker, they suffer from some drawbacks. The weak mechanical strength is the major shortcomings along with other drawbacks such as difficulty in large-scale preparation, instability of the product for long time performance, etc. In contrast, chemical cross-linking provides sufficient mechanical strength and stability along with large-scale preparation. During this method, either an additional cross-linking agent is used, or chemical modification of the polymeric chains is done to facilitate the cross-linking reaction. In the section, the various chemical cross-linking methods are discussed briefly.

(a) Chain growth polymerization

Chain growth polymerization of hydrogel preparation proceeds through free radical polymerization, which typically consists of three steps: (1) initiation, (2) propagation, and (3) chain termination. During initiation, free radicals are generated with exposure to light, heat, or redox conditions. In the propagation steps, the free radicals interact with the unsaturated double bonds propagating the chain and cross-linking occurs in the presence of a suitable cross-linker. The termination step occurs either by disproportionation, recombination, or other mechanism to stop the radicals from further propagation. Several types of chain growth polymerization process have been discussed in this section.

Solution polymerization

In this polymerization technique, neutral or ionic monomers dissolve with a solvent such as water, benzyl alcohol, ethanol, or an ethanol-water mixture. The polymerization process is initiated by using a redox or UV initiator and cross-linked by using a multifunctional cross-linker. This method is well known for ease of preparation, low cost, and uniform heat transfer during the polymerization process. Water is mostly used as a solvent during this polymerization process, and thus it is safe and harmless. The viscosity of the solution is generally low and thus stirring the reaction mixture is easy. Further, uniform heat transfer and dissipation occur unlike the bulk polymerization technique. The rate of polymerization is high with the potential to transform the homogeneous reaction mixture into a heterogeneous final product insoluble in monomer and the solvent used. The unreacted impurities present in the hydrogel can be separated by washing with distilled water [123].

Bulk polymerization

Bulk polymerization is one of the simplest polymerization techniques for hydrogel preparation. It involves the polymerization reaction between liquid monomers in presence of an initiator along with a cross-linker. Shin et al. used this technique to form a pH sensitive hydrogel [124]. AA was neutralized using NaOH and polymerized with hydroxyethyl methacrylate in the presence of MBA as a cross-linker and AIBN as the initiator. The polymerization reaction occurred at 75 °C within 30 min. Usually, this technique has a high polymerization rate and due to insufficient heat control, the viscosity of the reaction increases rapidly. Therefore, it is difficult to control the conversion rate to tune the properties of the hydrogel. The resulting product of this polymerization technique is glassy and transparent and swells in the presence of water [37]. However, by controlling the reaction temperature and concentration of the initiator the polymerization reaction can be controlled on a lab scale. But, in the case of large-scale processes, it becomes uneconomical and difficult task.

Emulsion polymerization (micellar polymerization)

Emulsion polymerization of hydrogel preparation includes a reaction between hydrophobic monomers, a surfactant, a water-soluble initiator, and a cross-linker. This technique can be easily controlled, as effective heat transfer is possible.

(b) Polymerization by irradiation

Various high-energy radiations such as electron beams and gamma rays have also been used as the initiators to synthesize hydrogels. The irradiation of the aqueous solution of polymer leads to the generation of radicals on the polymer and the radiolysis of water molecules results in hydroxyl radicals. These hydroxyl radicals also attack the polymer chains, resulting in a macro-radical. Recombination of the macro-radicals results in a covalently bonded cross-linked structure. Karadağ, et al., prepared an AM and itaconic acid-based hydrogel by irradiating using γ-rays. The hydrogel showed a maximum 2100 % swelling ability [125]. Similarly, Ajji et al., use an electron beam for the preparation of an agar, ethylene glycol, and poly(*N*-vinylpyrrolidone)-based hydrogel [126]. This technique leads to the generation of a relatively pure and cross-linker-free hydrogel.

(c) Grafting

In this technique, addition of a monomer occurs onto the backbone of a previously formed polymer, for example, polysaccharides. This method also involves a chemical initiator or high-energy radiation to initiate both the polymer chains and the monomers. The polymeric chains proceed via the initiation reaction and are grafted on the activated existing polymer chains resulting in a cross-linked gel in the presence of a cross-linker. It is one of the most widely used polymeric techniques with exciting properties. Grafting can be further categorized into two ways: graft copolymerization with/without the presence of a cross-linker.

In the case of graft polymerization without the use of a cross-linker, the OH groups of the polysaccharide units and the initiator (usually Ce^{4+} ions) interact to make redox pair-based complexes. These complexes are further dissociated to create radicals on the backbone of the polysaccharide through homogenous cleavage of C-C bonds. These free radicals initiate the polymerization of vinyl monomers and grafting occurs on the polysaccharide chains. Athawale et al. reported the grafting of AA on maize starch by using ceric ions as an initiator in an aqueous medium [127].

In the other method, initiation occurs at the hydroxyl groups of the polysaccharide units in presence of a thermal initiator or by irradiation. For instance, Pourjavadi et al. prepared a κ-carrageenan-based hydrogel by grafting AA in the presence of APS as the initiator and MBA as the cross-linker [128].

(d) Direct cross-linking by using cross-linker

Various mono-or polyfunctional small molecules are used to directly cross-link hydrogel through covalent bonding. Examples of these cross-linkers are added in the material section. Generally, covalently cross-linked hydrogels have higher toughness compared to the physically cross-linked hydrogel. Demitri et al. reported the preparation of critic acid cross-linked with cellulose based on anhydride intermediate formation [129]. Similarly, Song et al. prepared ECH cross-linked with cellulose with the high mechanical strength [101].

(e) IPN

An IPN is a polymer network consisting of two or more than two polymers that are partly interlaced at the molecular level but are not bonded covalently to each other. Although chemical bonds are not present within the networks, they cannot be pulled apart unless chemical bonds are broken. In other words, polymerizable monomers polymerize in the presence of polymer networks to form physically associated networks known as IPNs. There are two different types of IPN hydrogels. These are semi and full IPN. Both natural and synthetic polymer networks are used to prepare IPN-based hydrogels. Liu et al. prepared an IPN-based hydrogel by using gelatin and bi-functionalized dextran with aldehyde and methacrylate for tissue engineering application [130].

(f) Schiff base reaction

The Schiff base reaction discovered in 1864 by Hugo Schiff and it is a widely used chemical method for hydrogel formation. Schiff base has the structure $R_2C=N$ and is formed by the condensation reaction between carbonyl groups and a primary amine group. The reaction proceeds under mild conditions and water is the only byproduct of the reaction [49]. Qu et al. used this method to cross-link between *N*-carboxyethyl chitosan and dialdehyde PEG groups [131].

1.5. Characterization

To characterize the hydrogel after preparation and the respective changes that occur during various applications, different spectroscopic and microscopic techniques have been used. In the following subsections, a brief description of all these characterization techniques has been given.

1.5.1. Spectroscopic techniques

1.5.1.1. Fourier transforms infrared (FTIR) spectroscopy

FTIR spectroscopy is one of the most common spectroscopic techniques used to determine the different functional groups present in synthesized hydrogels. In this particular technique the molecules undergo vibrations due to the absorption of infrared electromagnetic radiation [132]. The presence of various polar functional groups such as hydroxyl (–OH), amine (–NH), and carbonyl (–C=O), etc. along with –CH, –C=C–, aromatic, etc. groups can be identified by using this technique. These groups absorb the IR radiation within 4000-400 cm^{-1} wavenumber and each group has a characteristic frequency. In the case of hydrogel, this technique is helpful to determine the presence of cross-linker having IR active groups. For example, the presence of MBA as a cross-linker can be determined from its characteristics IR absorption bands due to the presence of –NH groups [133]. Moreover, the formation or presence of ether linkages or ester linkages can also be determined by using this spectroscopic technique [134, 135]. In addition to this, the disappearance of several characteristics peaks after the reaction between two moieties also provides information about the progress of the reaction [101].

1.5.1.2. Ultraviolet-visible (UV-vis) spectroscopy

UV-vis spectroscopy is the most common and preliminary spectroscopic technique used to characterize the moieties having unsaturation and conjugation. These functional moieties are capable of absorbing UV-vis electromagnetic radiation within the range between 200-800 nm and exhibit $n\rightarrow\pi^*$, $\pi\rightarrow\pi^*$ and charge transfer transitions. Generally, this spectroscopic technique has not been directly utilized for the structural elucidation of hydrogels. But various application purposes such as photocatalytic degradation of various pollutants [136], dye adsorption on hydrogel [137], and extent of various reactions [138], etc. could be analyzed by using this technique.

1.5.1.3. X-ray photoelectron spectroscopy (XPS)

XPS is a non-destructive analytical technique utilized to determine the chemical composition of the material. This technique can also provide electronic structure along with the oxidation state of the materials based on their ionization energy. In this technique, a beam of the mono-energetic electron beam is irradiated, and the kinetic energies of the ejected electrons are quantified to obtain the required result [139]. Thus, this technique has widely been utilized for the structural elucidation of hydrogels. Further, the change in the chemical state of a hydrogel during its performance as well as the presence of different metals and hetero atoms is also detected by using this spectroscopic technique [140].

1.5.2. Microscopic techniques

1.5.2.1. Inverted microscopy (IM)

IM is a common microscopic technique used to visualize small particles of biological molecules. An IM is composed of a light source and condensers lenses at the top of the microscope and the objectives the placed below in an upward direction. This microscopic technique can be used to study the cell morphology to investigate the biocompatibility of hydrogels [141].

1.5.2.2. Scanning electron microscopy (SEM)

SEM is a vital microscopic technique used to study the surface topography of hydrogels. This technique can provide valuable information about the surface morphology along with the size and shape of the material [142]. To obtain the micrographs it scans the studied surface with a focused electron beam using electromagnetic lenses [143]. After hitting the surface, the high-energy electron beam scattered back to result in the SEM micrographs [144]. There are two types of scattering viz. elastic scattering and non-elastic. The electrons resulting from elastic scattering are known as back-scattered electrons, while electrons obtained from inelastic types of interaction are termed secondary electrons. To detect these electrons Everhart-Thornley detector (for secondary electrons) and solid-state detector (for backscattered electrons) are used. In recent years this microscopic technique has wide applicability in the surface morphology study of hydrogels. This technique is used by Thombare et al. to study the change in surface morphology of the biodegraded hydrogel by using a soil burial method [7].

1.5.2.3. Field emission scanning electron microscopy (FESEM)

FESEM is one of the most important microscopic techniques used to study the surface morphology with higher resolution and better image quality than SEM. These two techniques mainly differ due to the difference in their electron-producing system. In the case of SEM, a thermal source (heated tungsten filament) is used for the ejection of the electron, whereas in FESEM, a field emission gun is used to generate the electron beams. The highly focused electron beam produced in the FESEM process lower energy and can improve the resolution power of the microscopic images. This technique is used to study the change in morphology of the hydrogels after a foreign element is get entrapped in their surface during service. Bhatia et al. used FESEM to study the change in surface morphology of the hydrogel after the adsorption of metal ion [145].

1.5.3. Other techniques

1.5.3.1. Thermogravimetric analysis (TGA)

TGA determines the thermal degradation of a material by measuring the weight loss as a function of temperature under an open or an inert atmosphere [146]. Along with thermal stability, this technique can provide several important information including phase transition, adsorption, desorption, degradation kinetics, etc. Moreover, the first derivatives (DTG) of TGA give information about the initial and final degradation temperature, maximum degradation temperature, and degradation pattern. This technique also helps to identify the thermally labile linkage present in the sample along with the presence of fillers, plasticizers, and volatiles [147]. TGA is extensively used by various researchers for the determination of the thermal stability of different hydrogels [148,149].

1.5.3.2. Differential scanning calorimetry (DSC)

DSC determines the thermal properties of a polymeric sample including melting temperature (Tm), glass transition temperature (Tg), specific heat, and crystallization, etc. In this colorimetric technique, the samples are heated up to their melting temperature and thereafter cooling under an inert atmosphere to obtain the physico-chemical changes of the material with respect to the heat flow and change in temperature [150]. This analysis was used to study the thermal properties of Gum tragacanth-sodium alginate-based hydrogel by Singh et al. [151].

1.6. Testing methods

1.6.1. Swelling ability

The swelling ability of the synthesized hydrogels is determined by immersing the dry hydrogels in an excess liquid medium. After, equilibrium absorption, the increase in weight with respect to the initial weight was determined to obtain the swelling ability of the hydrogels.

1.6.2. Mechanical testing methods

The mechanical properties of the hydrogels such as tensile strength, and elongation at break of the synthesized mechanically tough hydrogels are determined using the Universal Testing Machine (UTM) with accordance to the standard ASTM D882-12 method. In this particular technique, a rectangular hydrogel with a particular dimension suitable for the UTM machine is pulled apart with a calculated amount of load up to which the hydrogel can bear the load [152] (ASTM D882-12).

1.6.3. Biological testing methods

1.6.3.1. Cytotoxicity study

Cytotoxicity is one of the most widely used methods to determine the toxicity level of any materials, In this methods human cells are allowed to grow in a suitable medium in a suitable temperature (usually 37 °C) in the presence of CO_2 atmosphere. The grown cells were treated with the sample for cytoxicity study for a predetermine time followed by the treatment with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). In the presence of metabolically active cells, MTT converted to a dark purple formazan. This formazan is dissolved in a denaturing buffer solution and the cell viability is determined by measuring the absorbance at 570 nm wavelength [153].

1.6.3.2. Antibacterial test

Generally, “Agar well diffusion” method is used to determine the antimicrobial activity of hydrogels [154]. In this method, Petri dishes containing potato dextrose agar or Muller-Hinton agar are inoculated with inoculum of test microbes (bacteria, fungi, etc.). Then the hydrogel solutions with desired concentration are placed on the agar surface. To create wells a cork borer with 6 mm diameter is used. The antimicrobial agent diffuses into the agar and inhabits the germination and growth of the microorganism. A standard antibacterial solution is used as a positive control. Then the agar plates are incubated for a specific period at a constant temperature [155]. After, a predetermined time interval the diameter of the inhibition of zone of the test samples is compared with the diameter of the control to justify the superiority/inferiority.

1.6.4. Biodegradation test

The biodegradation test of the synthesized hydrogels was done by using soil burial method. In this method, a particular volume of dry hydrogels was kept under the soil for degradation. After a particular time-interval, the weight loss of the hydrogels was measured along with SEM image analysis of the hydrogel surface.

1.7. Property

Hydrogels possess a wide range of versatile properties that make them suitable for different application purposes. A few important properties of hydrogels are summarized in the following section.

1.7.1. Swelling

Swelling is the intrinsic property of hydrogels. In other words, the identity of hydrogel is defined by water absorption ability. Swelling is defined as the increase in weight of the swollen gel to the dry gel after the adsorption of the liquid medium. When a dry hydrogel comes in contact with water, the water molecules hydrated the most polar, hydrophilic groups leading to the penetration of liquid molecules inside the 3D network. After the polar and hydrophilic groups get hydrated, they can imbibe additional water molecules due to the difference between the osmotic pressure inside and outside of the gel. This imbibed water fills the space inside the micro or macro pores present in the hydrogel matrix [40]. The presence of physically or chemically cross-linked points prevents the 3D network to swell up to infinity and thereby restricting the dissolution of the hydrogel in the liquid medium. Moreover, the elastic contraction force also prevents the complete solubilization of the gel and thereby remaining in the originally coiled shape along with the absorbed water [156,157]. In short, the swelling process of hydrogel involves three steps: the first one is the diffusion of water molecules inside the 3D network; in the second step the loosening of polymeric chains occurs and finally, the expansion of the network occurs [36]. Moreover, the imbibed water molecules serve as a selective filter for the diffusion of other molecules dissolve in the liquid medium [40]. Hence, in addition to water, they are also able to absorb various physical solutions such as brines, and electrolyte solutions as well as many biological solutions like sweat, urine, blood, etc. Moreover, the swelling ability and rate are dependent on various parameters including porosity, particle size, drying procedure, and the structure of the polymeric network [30]. The swelling amount is also affected by the cross-linking density, as highly cross-linked structures possess a lower swelling ability and vice versa. However, chemical structure has also a significant effect, hydrogels containing more hydrophilic groups swell more compared to hydrophobic moieties. Depending on these properties, hydrogels can absorb water from a very lower amount (less than 10 g/g) to several hundred times higher than their dry weight (2000 g/g). Literature advocates the presence of numerous highly swellable hydrogels by using different hydrophilic moieties. In 2006, El-Mohdy et al. prepared a starch and AA-based hydrogel with 350 g/g water absorption ability [158]. A carboxymethylcellulose (CMC) and cellulose-based hydrogel were synthesized by Chang et al. in NaOH and urea aqueous solution by using ECH as a cross-linker. The hydrogel exhibits an exciting swelling ability of 1000 times greater than the dry weight and the presence of CMC contributed to enhancement in the pore size of the hydrogel [100].

1.7.1.1 Deswelling and reswelling ability

Deswelling and reswelling are important properties of hydrogel for its recyclability in practical applications. With exposure to heat, hydrogels start to deswell the imbibed liquid from its 3D network. But even after deswelling, the hydrogel can again undergo reswelling and have the ability to undergo repeated swelling-deswelling cycles. In 1995, Yan et al. synthesized a macroporous hydrogel with rapid swelling and deswelling ability [159].

1.7.1.2. Saline sensitivity

The swelling ability of hydrogels is critically dependent on the ionic strength of the liquid medium. Upon increase in salt concentration, the swelling capacity of the hydrogel decreased due to the reduction of osmotic pressure as well as precipitation of the hydrogel in salt solution [25].

1.7.1.3. pH sensitivity

Hydrogels containing acidic groups such as carboxylic acid, sulfonic acid, etc., and hydrogels containing basic groups such as amines, amides, etc. exhibit pH-sensitive swelling ability. With the change in pH, these groups become ionized by accepting and releasing protons. Anionic hydrogels such as poly(acrylic acid) (PAA)-based hydrogels are deprotonated in an acidic environment and the electrostatic repulsion of the ionic groups increases and thus allows penetration of larger number of water molecules into the 3D network of the hydrogel [160]. While in an acidic medium, the anionic hydrogels protonate resulting in a decrement in charge density and collapse of the polymer chains. In contrast, cationic hydrogels exhibit high swelling ability in acidic pH, and shrinkage of the gel structure occur at basic pH condition. For example, chitosan-based hydrogel showed pH-sensitive swelling ability and higher swelling ability is observed at lower pH [161].

1.7.2. Cross-linking

Cross-linking cannot be defined as the property of a hydrogel, but it is indeed the cause for all the properties of hydrogel; directly or indirectly. A small change in cross-linker amount can differ a lot. To attain the hydrogel network various kinds of cross-linking approaches have been adopted by various researchers. This includes chemically, physically, or both chemically and physically cross-linking strategies, and so on [63]. By regulating the extent of cross-linking, it is possible to modify the various properties of hydrogel and customized it for a targeted application. Thus, a wide applicability can be achieved from the same original polymer [162, 163].

1.7.3. Biocompatibility

Several hydrogels process adequate biocompatibility and this property makes them pertinent in biomedical fields. For biomedical use, the material should pass in vivo toxicity test and it must be non-cytotoxic. The term biocompatibility can be defined with respect to two parameters; firstly, biosafety and the other one is bio-functionality. The material should be nontoxic not only for the system, but also safe for the surrounding tissues as well. Literature advocates the synthesis of numerous hydrogels with extraordinary biocompatibility and nontoxicity for biomedical uses including controlled drug delivery [8], tissue engineering [9], biosensing [164], etc. Moreover, the term bio-functionality can be used to define the capacity of the material to achieve the special task for which it is intended. Along with biocompatibility, hydrogels possess a controlled release ability of the encapsulated material which makes it suitable for sustained drug delivery applications. Moreover, due to their structural similarities with the natural tissues, they achieve the properties to act as a scaffold for tissue engineering applications.

1.7.4. Biodegradability

The biodegradability of hydrogels means the breakdown of the 3D network into harmless end products by various living organisms under open atmospheric conditions. It depends on the starting materials and the methods used for hydrogel preparation. Usually, polysaccharide-based hydrogels are easily biodegradable, but a few synthetic polymers also exhibit biodegradability. The biodegradation process includes the hydrolysis and solubilization of fragmented moieties into nontoxic end products. Biodegradation of hydrogels can be done either in the accelerated condition in presence of bacterial strains or by using soil burial methods. The microorganisms present in the systems excrete extracellular enzymes which hydrolyze the chemical bonds of the hydrogels leading to surface erosion and the degradation of the gel networks. Due to the high biodegradability of the polysaccharides, it is easy for the microorganism to hydrolyze them and turn the hydrogel network into smaller and lower molecular weight fragments. With exposure for a longer time, the fragments are further converted to humus, water and CO_2 by the use of some metabolic pathways. Thus, typical biodegradation of hydrogels includes absorption of water, cleavage of the biodegradable moieties to smaller fragments, and lastly engulfment of the small fragments by microorganisms. The biodegradation of hydrogels depends on various factors such as molecular weight, hydrophilicity, hydrogel-water interaction, etc. Several environmental factors such as temperature, pH, humidity, rainfall, wind flow and soil properties in the case of soil burial tests affect the rate of degradation. Biodegradability is one of the most essential factors and several biodegradable hydrogels have been reported by various researchers over the last few decades. Thombare et al. synthesized a guar-gum-based biodegradable hydrogels to act as a soil conditioner. The utilization of biodegradable hydrogels is of utmost importance in the biomedical field and several biodegradable hydrogels were synthesized for this purpose [7]. Sun et al. synthesized a hemicellulose-based biodegradable hydrogel for a controlled drug delivery system [165]. Similarly, Zhu et al. synthesized an antibacterial hydrogel with biodegradable properties for wound dressing application [166].

1.7.5. Mechanical property

Usually, conventional hydrogels are mechanically weak due to their irregular molecular weights and uneven cross-linking patterns. But several applications demand the mechanical stability of hydrogel for its smooth performance. The assessment of mechanical strength is of utmost significant for various applications such as biomedical including tissue engineering, wound dressing, cartilage repair, etc. Along with these, mechanical strength is also important for wastewater treatment, sensing, and electric applications of hydrogels. It is one of the most important requirements that the hydrogel must retain its physical structure during a performance at least for a specific period. Various synthetic strategies such as double cross-linking [35], nanocomposite hydrogels [167], and hydrophobically associated hydrogels, [168], etc. are utilized to obtain a mechanically tough hydrogel.

Cross-linking density is one of the most important parameters which affect the mechanical strength of hydrogel enormously. Generally, higher mechanical strength is obtained with an increase in cross-linking degree. However, too much high cross-linking density decreases the elongation and elasticity of the gel network. Thus, an optimum cross-linking density is required for the flexibility of the gel with high mechanical strength [36].

1.7.6. Shape memory property

Shape memory hydrogels represent an interesting class of smart materials that can recover their permanent shape after deformation in the absence or the presence of an appropriate stimulus. These types of material exhibit an internal structural rearrangement to recover the permanent shape achieve by cross-linking of the polymeric backbone. Thus, to achieve shape memory properties the hydrogel should be programmed to contain a physical or chemical or memory code to recover into the original shape of the matrix [169]. During the deformation process, some networks of shape memory hydrogels maintain permanent shape, and dynamic networks are applied for shape memory [170].

Generally, this “smart” behavior of polymeric materials can be achieved in response to various external stimuli such as light, heat, or electricity. However, this property can also be achieved without any stimulus. For example, Chen et al., synthesize a fully physically cross-linked hydrogel with self-recovery property without any external stimuli [63]. Now a day, shape memory hydrogels have attracted increasing attention because of their potential applications such as biomedical, soft robotics, artificial muscles, etc. [170].

1.7.7. Self-healing ability

Self-healing property is the most unique property which provides automatic healing ability of the damage zone to restore normality with or without the presence of external stimuli. The external stimuli which provide self-healing behavior are heat, pH, chemical healing agents, and microwave assistant healing ability, etc. However, stimulus-independent healing ability is more advantageous and gain more attention in recent times [171]. Self-healing hydrogels can be obtained by both physical and chemical cross-linking mechanisms. Chemically self-healed hydrogels reform the damage zone via reversible chemical networks such as disulfide bonds, dynamic imine bonds, phenyl boronic ester bonds, etc. Physically cross-linked self-heal hydrogels can re-establish the network through various dynamic non-covalent interactions including hydrogen bonding, hydrophobic interaction, host-guest interaction, etc. For both types of healing processes, there must have some specific functional groups with desired chemical properties to mediate the healing process of the damage zones [172].

1.8. Applications

The versatile properties and the specific structures of hydrogels make them suitable for numerous applications ranging from industrial to biomedical fields. Some major applications and some examples of hydrogel usages are listed herein to define the importance of these materials.

1.8.1. Biomedical fields

Apart from high swelling ability, versatile properties like soft nature, flexibility, stimuli-responsive, resemblance to living tissues, porous structure, biocompatibility and biodegradability, make hydrogels suitable for various biomedical applications. Moreover, tunable physicochemical properties, ease of preparation as well as usage, immunogenicity, and structural varieties such as solid, liquid, semi-solid, etc. are also advantageous properties for these fields [173]. Hydrogels have wide applicability in various domains of biomedical fields as discussed subsequently.

1.8.1.1. Controlled release of therapeutic agents

One of the most promising biomedical applications of hydrogel is the controlled release of therapeutic agents to achieve an effective rate at the targeted site. The increasing demand for the material in drug delivery systems is due to its highly swellable porous 3D network structure. This property supports holding different drugs molecule inside the network and release of these encapsulated drugs in a controlled manner. Moreover, hydrogel also offers various stimuli-responsive controlled release abilities such as pH, magnetic field, temperature, etc. Amin et al. synthesized a thermo- and pH-sensitive drug delivery system by using bacterial cellulose and AA [174]. Lin et al. prepared a magnetic response drug release system by using cellulose and Fe_3O_4 nanoparticles to obtain the controlled release ability of 5-fluorouracil [175]. The hydrogel exhibits fast swelling and deswelling ability in the presence of an external magnetic field and offers remotely control drug release. The hydrogel exhibits stepwise drug release, and the rate can be controlled by switching on-off the magnetic field.

1.8.1.2. Tissue engineering

The highly hydrated 3D network of hydrogels received extensive importance in tissue engineering due to their structural and compositional similarities with the extracellular matrixes of various tissues. The amazing biocompatibility, highly swollen network, mass transfer ability, and encapsulation of biomolecules and cells into the 3D network are also the most appropriate property which makes these materials suitable for tissue engineering applications [176]. These properties are affected by the nature and molecular arrangement of the polymeric chains, the degree of cross-linking, and the swelling ability of the gel. The interconnected pores of hydrogel permit cell infiltration and deployment and also enhanced the surface area for cell attachment and interaction. For tissue engineering applications, hydrogels are used as 3D networks that arrange cells and provide stimuli as a space-filling agent to form a desired tissue and as delivery agents for various bioactive molecules [176]. Hydrogel scaffolds are widely utilized in the regeneration of cartilage, cardiac tissues, and bone. Fan et al. reported a mechanically tough methacrylated hyaluronic acid-based double network hydrogel for cartilage tissue engineering [177]. In another study, Nie et al. reported a biphasic calcium phosphate nanoparticle incorporated hydroxyethyl chitosan/PVA hydrogel for bone regeneration [178].

1.8.1.3. Wound dressing

Along with other biomedical applications, hydrogels received immense importance as a dressing material in the affected wound. Hydrogels can provide a moist environment and enhanced oxygen transportation in the affected area to the facilitated healing process. Due to the high absorption capacity, it can remove the blood, exudates, etc. [177] and also can exhibit slow release of antibiotics to provide protection against bacterial infections. Das et al. synthesized a mechanically tough, starch and PVA-based hydrogel by using critic acid as both plasticizer and cross-linker, and glycerol was used to provide film flexibility [178]. The hydrogel can show antibacterial activity for bacterial strain and exhibit notable water vapor transmission ability. In another work, a hyaluronic acid-based dressing material was synthesized by Liang et al. with multiple properties such as adhesive, hemostatic, antioxidant, and conductivity [179].

1.8.1.4. Contact lenses

The applicability of hydrogel as contact lenses was first discovered by Wichterle and Lim in 1960. Later, hydrogels based on different hydrophilic polymers such as PVA, poly(acrylonitrile), etc. have been investigated for contact lenses applications. Now a day, silicon-based hydrogels play a dominant role as contact lenses [180]. Hydrogels exhibit all the essential properties for contact lenses such as high-water content, oxygen permeability, water transfer ability, etc. Apart from these, the material should be biocompatible, non-irritable, continuous tear film for clear vision, and comfortable to wear, etc. Due to the presence of almost all the properties, hydrogels have found wide applicability in this field [173].

1.8.2. Wastewater treatment

The highly hydrophilic, porous, three-dimensional network of hydrogel enables them to capture the toxic metal ions and dyes from the aqueous medium for wastewater treatment. The additions of pullulated water from various industries such as paints, textile, battery manufacturing industry, pharmaceuticals, etc. contain various dyes and toxic metal ions. At very minute concentrations, these pollutants can cause a notorious effect on the ecosystem and human health [11]. During water absorption, the pollutants also penetrate inside the 3D network of the hydrogel matrix. The presence of various charged or neutral functional groups act as complexing agents with the pollutants present in the aqueous solutions. Due to the insoluble nature of hydrogel in water, the hydrogel after complexation with the pollutants can be easily removed from the aqueous medium [10].

1.8.3. Agricultural field

Taking the advantages of high-water absorption capacity, hydrogels have found wide applicability as a soil conditioner and water holding agent of soil in agriculture. The encapsulation ability of nutrients and controlled release of them with time is one of the most useful properties to reduce to leach out fertilizer in agricultural fields. Thus, hydrogels having these properties along with adequate biodegradability have been widely used for agricultural applications. For example, Thombareet al. synthesized a guar gum based hydrogel for agricultural application with the potential to enhance the water holding capacity of soil along with the increment in porosity and moisture retention and absorption capacity [7]. For controlled release of fertilizer, Xiao et al. utilized starch-based hydrogel and found controlled release ability of urea up to 45 days [6].

1.8.4. Miscellaneous applications

In the recent era hydrogels receive remarkable progress on energy and energy related applications due to their diverse property. The desirable swelling ability, mechanical stability, ionic/electronic conductivities, stimuli-responsiveness, are the key properties which makes hydrogels suitable for the energy sector. In addition to these properties, the flexible structure, self-healing ability, electrolyte permeability, shape memory, etc. offers versatile energy related applications such as super capacitors, flexible batteries, wearable devices, etc. Moreover, the large surface area and massive active sites for electrocatalysis reactions offers enormous potential for different applications such as fuel cells, metal-air batteries, etc [13]. Moreover, hydrogels based materials also widely used in hygienic applications such as formation of baby or adult diapers.

1.9. Scopes and objectives of the present investigation

Based on the state of art literature mentioned in this chapter, it can be elucidated that enormous works have been performed on polysaccharide-based hydrogels and there are lots of ongoing research in these fields. Although, the research on hydrogels is receiving a sky-high status, but in this growing scientific world there are always scopes for new achievements and thus huge opportunities to meet some unmet demands are still waiting. Though lots of works on the fabrication of polysaccharide-based superabsorbent hydrogels, literatures on starch-based high swell able hydrogels with small volume of synthetic monomers are very limited. Moreover, there is very less work on starch-based amphoteric hydrogels. Also, there is a lack of research work on polysaccharide-based double cross-linked hydrogel with high mechanical toughness. In addition to this, literature remains almost silent on starch-based self-healing hydrogels with swelling-induced mechanical strength. Although, several works on the utilization of hydrogels for in-vivo drug release study, but fabrication of tunable stimuli-responsive controlled drug release systems are limited in the literature. Further, literature also remains silent on fully bio-based tough hydrogels with swelling-induced mechanical strength suitable for dressing applications. Thus, despite of the numerous researches, there are still some gaps in the existing work. Hence, the scope of the research work is to overcome some of the drawbacks of recent hydrogel research to enrich the applicability of the materials in numerous fields.

Thus, keeping all these facts in mind, the following objectives have been isolated for the present investigations.

i) To synthesize bio-based environmentally benign hydrogels using different polysaccharides and synthetic monomers like AA, AM, etc.

ii) To characterize the synthesized polysaccharide-based hydrogels using different spectroscopic and analytical techniques.
iii) To evaluate the properties like water absorbency, metal and dye adsorption ability, self-healing ability, controlled release ability, amphoteric property, toughness, stimuli responsive swelling ability, swelling induced mechanical strength, etc.
iv) To utilize the hydrogels in the fields of controlled release fertilizer, soil conditioner, wastewater treatment, biomedical, etc.

1.10. Plan of research

In order to execute the proposed objectives, the research work is planned in the following ways.

i) A thorough literature survey would be conducted in the field of polysaccharide-based hydrogels.
ii) Bio-based hydrogels would be synthesized using bio-based raw materials via environmentally benign routes.
iii) Various stoichiometric ratios of the reactants would be used to optimize the performance of the hydrogel and the best composition would be applied for further study.
iv) The synthesized hydrogels would be characterized by using various analytical and spectroscopic techniques such as FTIR, XPS, TGA, DSC, etc.
v) The performance of the synthesized hydrogels would be investigated by examining the properties like swelling ability, amphoteric property, toughness, self-healing ability, stimuli responsive swelling ability, swelling induced mechanical strength, etc.
vi) The best studied hydrogels with optimum amount of all the reactants would be utilized for potential applications such as controlled release of fertilizer, soil conditioner, dye and metal ion adsorbent, mechanically strong self-healing material, controlled drug delivery system, etc.

References

[1] Karak, N. *Fundamentals of Polymers*, PHI Learning Pvt. Ltd., New Delhi, 2009.

[2] Thakur, V. K. and Thakur, M. K. Recent trends in hydrogels based on psyllium polysaccharide: a review. *Journal of Cleaner Production*, 82:1-15, 2014.

[3] Yu, H., Lu, J., and Xiao, C. Preparation and properties of novel hydrogels from oxidized konjac glucomannan cross-linked chitosan for in vitro drug delivery. *Macromolecular Bioscience*, 7(9-10):1100-1111, 2007.

[4] Cheng, B., Pei, B., Wang, Z., and Hu, Q. Advances in chitosan-based superabsorbent hydrogels. *RSC Advances*, 7(67):42036-42046, 2017.

[5] Zohourian, M. M. and Kabiri, K. Superabsorbent polymer materials: a review. *Iranian Polymer Journal*, 17(6):451-477, 2008.

[6] Xiao, X., Yu, L., Xie, F., Bao, X., Liu, H., Ji, Z., and Chen, L. One-step method to prepare starch-based superabsorbent polymer for slow release of fertilizer. *Chemical Engineering Journal*, 309:607-616, 2017.

[7] Thombare, N., Mishra, S., Siddiqui, M. Z., Jha, U., Singh, D., and Mahajan, G. R. Design and development of guar gum based novel, superabsorbent and moisture retaining hydrogels for agricultural applications. *Carbohydrate Polymers*, 185:169-178, 2018.

[8] Tripodo, G., Trapani, A., Rosato, A., Di Franco, C., Tamma, R., Trapani, G., and Mandracchia, D. Hydrogels for biomedical applications from glycol chitosan and PEG diglycidyl ether exhibit pro-angiogenic and antibacterial activity. *Carbohydrate Polymers*, 198:124-130, 2018.

[9] Yang, Y., Ritchie, A. C., and Everitt, N. M. Comparison of glutaraldehyde and procyanidin cross-linked scaffolds for soft tissue engineering. *Materials Science and Engineering: C*, 80:263-273, 2017.

[10] Shalla, A. H., Yaseen, Z., Bhat, M. A., Rangreez, T. A., and Maswal, M. Recent review for removal of metal ions by hydrogels. *Separation Science and Technology*, 54(1):89-100, 2019.

[11] Bello, K., Sarojini, B. K., Narayana, B., Rao, A., and Byrappa, K. A study on adsorption behavior of newly synthesized banana pseudo-stem derived superabsorbent hydrogels for cationic and anionic dye removal from effluents. *Carbohydrate Polymers*, 181:605-615, 2018.

[12] Cascone, S. and Lamberti, G. Hydrogel-based commercial products for biomedical applications: A review. *International Journal of Pharmaceutics*, 573:118803, 2020.

[13] Guo, Y., Bae, J., Fang, Z., Li, P., Zhao, F., and Yu, G. Hydrogels and hydrogel-derived materials for energy and water sustainability. *Chemical Reviews*, 120(15):7642-7707, 2020.

[14] Shojaeiarani, J., Bajwa, D., and Shirzadifar, A. A review on cellulose nanocrystals as promising biocompounds for the synthesis of nanocomposite hydrogels. *Carbohydrate Polymers*, 216:247-259, 2019.

[15] Ferreira, S. S., Passos, C. P., Madureira, P., Vilanova, M., and Coimbra, M. A. Structure–function relationships of immunostimulatory polysaccharides: A review. *Carbohydrate Polymers*, 132:378-396, 2015.

[16] Zhu, T., Mao, J., Cheng, Y., Liu, H., Lv, L., Ge, M., and Lai, Y. Recent progress of polysaccharide-based hydrogel interfaces for wound healing and tissue engineering. *Advanced Materials Interfaces*, 6(17):1900761, 2019.

[17] Coutinho, P. M., Deleury, E., Davies, G. J., and Henrissat, B. An evolving hierarchical family classification for glycosyltransferases. *Journal of Molecular Biology*, 328(2):307-317, 2003.

[18] Ismail, H., Irani, M., and Ahmad, Z. Starch-based hydrogels: present status and applications. *International Journal of Polymeric Materials and Polymeric Biomaterials*, 62(7):411-420, 2013.

[19] Chang, C. and Zhang, L. Cellulose-based hydrogels: Present status and application prospects. *Carbohydrate Polymers*, 84(1):40-53, 2011.

[20] Chen, H., Yang, F., Hu, R., Zhang, M., Ren, B., Gong, X., and Zheng, J. A comparative study of the mechanical properties of hybrid double-network hydrogels in swollen and as-prepared states. *Journal of Materials Chemistry B*, 4(35):5814-5824, 2016.

[21] Pakdel, P. M. and Peighambardoust, S. J. Review on recent progress in chitosan-based hydrogels for wastewater treatment application. *Carbohydrate Polymers*, 201:264-279, 2018.

[22] Tønnesen, H. H., and Karlsen, J. Alginate in drug delivery systems. *Drug Development and Industrial Pharmacy*, 28(6):621-630, 2002.

[23] Buwalda, S. J., Boere, K. W., Dijkstra, P. J., Feijen, J., Vermonden, T., and Hennink, W. E. Hydrogels in a historical perspective: From simple networks to smart materials. *Journal of Controlled Release*, 190:254-273, 2014.

[24] Yahia, L., Chirani, N., Gritsch, L., Motta, F. L., and Fare, S. History and applications of hydrogels. *Journal of Biomedical Sciences*, 4(2):1-23, 2015.

[25] Buchholz, F.L. and Graham A.T. *Modern superabsorbent polymer technology*. Wiley-VCH, New York, 1998.

[26] Wichterle, O. and Lim, D. Hydrophilic gels for biological use. *Nature*, 185(4706):117-118, 1960.

[27] Macret, M. and Hild, G. Hydroxyalkyl methacrylates: hydrogel formation based on the radical copolymerization of 2-hydroxyethylmethacrylate and 2,3-dihydroxypropylmethacrylate. *Polymer*, 23(5):748-753, 1882.

[28] Schild, H. G. Poly (N-isopropylacrylamide): experiment, theory and application. *Progress in Polymer Science*, 17(2):163-249, 1992.

[29] Heskins, M., and Guillet, J. E. Solution properties of poly (N-isopropylacrylamide). *Journal of Macromolecular Science-Chemistry*, 2(8):1441-1455, 1968.

[30] Kabiri, K., Omidian, H., Zohuriaan-Mehr, M. J., and Doroudiani, S. Superabsorbent hydrogel composites and nanocomposites: a review. *Polymer Composites*, 32(2):277-289, 2011.

[31] Fanta, G. F., Burr, R. C., and Doane, W. M. Absorbents from Saponified Starch-g-poly(acrylonitrile-co-2-acrylamido-2-methyl-propanesulfonic acid). Some Practical Considerations. *Starch-Stärke*, 39(9):322-325, 1987.

[32] Danno, A. Gel formation of aqueous solution of polyvinyl alcohol irradiated by gamma rays from cobalt-60. *Journal of the Physical Society of Japan*, 13(7):722-727. 1958.

[33] Gimenez, V., Mantecon, A., and Cadiz, V. Modification of poly (vinyl alcohol) with acid chlorides and crosslinking with difunctional hardeners. *Journal of Polymer Science Part A: Polymer Chemistry*, 34(6):925-934, 1996.

[34] Peppas, N. A., and Berner Jr, R. E. Proposed method of intracopdal injection and gelation of poly (vinyl alcohol) solution in vocal cords: polymerconsiderations. *Biomaterials*, 1(3):158-162, 1980.

[35] Gong, J. P., Katsuyama, Y., Kurokawa, T., and Osada, Y. Double-network hydrogels with extremely high mechanical strength. *Advanced Materials*, 15(14):1155-1158, 2003.

[36] Bashir, S., Hina, M., Iqbal, J., Rajpar, A. H., Mujtaba, M. A., Alghamdi, N. A., and Ramesh, S. Fundamental concepts of hydrogels: Synthesis, properties, and their applications. *Polymers*, 12(11):2702, 2020.

[37] Ahmed, E. M. Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research*, 6(2):105-121, 2015.

[38] Dragan, E. S. Design and applications of interpenetrating polymer network hydrogels. A review. *Chemical Engineering Journal*, 243:572-590, 2014.

[39] Ali, A., and Ahmed, S. Recent advances in edible polymer based hydrogels as a sustainable alternative to conventional polymers. *Journal of Agricultural and Food Chemistry*, 66(27):6940-6967, 2018.

[40] Garg, S., Garg, A., and Vishwavidyalaya, R. D. Hydrogel: classification, properties, preparation and technical features. *Asian Journal of Biomaterial Research*, 2(6):163-170, 2016.

[41] Zhao, D., Huang, J., Zhong, Y., Li, K., Zhang, L., and Cai, J. High-strength and high-toughness double-cross-linked cellulose hydrogels: a new strategy using sequential chemical and physical cross-linking. *Advanced Functional Materials*, 26(34):6279-6287, 2016.

[42] Heidarian, P., Kouzani, A. Z., Kaynak, A., Paulino, M., Nasri-Nasrabadi, B., Zolfagharian, A., and Varley, R. Dynamic plant-derived polysaccharide-based hydrogels. *Carbohydrate Polymers*, 231:115743, 2020.

[43] Fan, Y. and Picchioni, F. Modification of starch: a review on the application of “green” solvents and controlled functionalization. *Carbohydrate Polymers*, 241:116350, 2020.

[44] Tester, R. F., Karkalas, J., and Qi, X. Starch-composition, fine structure and architecture. *Journal of Cereal Science*, 39(2):151-165, 2004.

[45] Han, Z., Zeng, X. A., Fu, N., Yu, S. J., Chen, X. D., and Kennedy, J. F. Effects of pulsed electric field treatments on some properties of tapioca starch. *Carbohydrate Polymers*, 89(4):1012-1017, 2012.

[46] Lu, D. R., Xiao, C. M., and Xu, S. J. Starch-based completely biodegradable polymer materials. *Express Polymer Letters*, 3(6):366–375, 2009.

[47] Qamruzzaman, M., Ahmed, F., Mondal, M., and Ibrahim, H. An overview on starch-based sustainable hydrogels: Potential applications and aspects. *Journal of Polymers and the Environment*, 30:19-50, 2022.

[48] Hamedi, H., Moradi, S., Hudson, S. M., and Tonelli, A. E. Chitosan based hydrogels and their applications for drug delivery in wound dressings: A review. *Carbohydrate Polymers*, 199:445-460, 2018.

[49] Muir, V. G., and Burdick, J. A. Chemically modified biopolymers for the formation of biomedical hydrogels. *Chemical Reviews*, 121(18):10908-10949, 2020.

[50] Gómez-Ríos, D., Barrera-Zapata, R., and Ríos-Estepa, R. Comparison of process technologies for chitosan production from shrimp shell waste: A techno-economic approach using Aspen Plus®. *Food and Bioproducts Processing*, 103:49-57, 2017.

[51] Di Martino, A., Sittinger, M., and Risbud, M. V. Chitosan: a versatile biopolymer for orthopaedic tissue-engineering. *Biomaterials*, 26(30):5983-5990, 2005.

[52] Yin, Z. C., Wang, Y. L., and Wang, K. A pH-responsive composite hydrogel beads based on agar and alginate for oral drug delivery. *Journal of Drug Delivery Science and Technology*, 43:12-18, 2018.

[53] Fu, L. H., Qi, C., Ma, M. G., and Wan, P. Multifunctional cellulose-based hydrogels for biomedical applications. *Journal of Materials Chemistry B*, 7(10):1541-1562, 2019.

[54] Kabir, S. M., Sikdar, P. P., Haque, B., Bhuiyan, M. A., Ali, A., and Islam, M. N. Cellulose-based hydrogel materials: Chemistry, properties and their prospective applications. *Progress in Biomaterials*, 7(3):153-174, 2018.

[55] Sharma, G., Sharma, S., Kumar, A., Ala'a, H., Naushad, M., Ghfar, A. A., and Stadler, F. J. Guar gum and its composites as potential materials for diverse applications :A review. *Carbohydrate Polymers*, 199:534-545, 2018.

[56] Burdick, J. A. and Prestwich, G. D. Hyaluronic acid hydrogels for biomedical applications. *Advanced Materials*, 23(12):H41-H56, 2011.

[57] Singh, R. S., Kaur, N., Rana, V., and Kennedy, J. F. Pullulan: A novel molecule for biomedical applications. *Carbohydrate Polymers*, 171:102-121, 2017.

[58] Das, D. and Pal, S. Modified biopolymer-dextrin based crosslinked hydrogels: application in controlled drug delivery. *RSC Advances*, 5(32):25014-25050, 2015.

[59] Osmałek, T., Froelich, A., and Tasarek, S. Application of gellan gum in pharmacy and medicine. *International Journal of Pharmaceutics*, 466(1-2):328-340, 2014.

[60] Yuan, M., Bi, B., Huang, J., Zhuo, R., and Jiang, X. Thermosensitive and photocrosslinkable hydroxypropyl chitin-based hydrogels for biomedical applications. *Carbohydrate Polymers*, 192:10-18, 2018.

[61] Freier, T., Montenegro, R., Koh, H. S., and Shoichet, M. S. Chitin-based tubes for tissue engineering in the nervous system. *Biomaterials*, 26(22):4624-4632, 2005.

[62] Giri, T. K., Thakur, A., Alexander, A., Badwaik, H., and Tripathi, D. K. Modified chitosan hydrogels as drug delivery and tissue engineering systems: present status and applications. *Acta Pharmaceutica Sinica B*, 2(5):439-449, 2012.

[63] Chen, Q., Zhu, L., Chen, H., Yan, H., Huang, L., Yang, J., and Zheng, J. A novel design strategy for fully physically linked double network hydrogels with tough, fatigue resistant, and self-healing properties. *Advanced Functional Materials*, 25(10):1598-1607, 2015.

[64] Walimbe, T., Panitch, A., and Sivasankar, P. M. A review of hyaluronic acid and hyaluronic acid-based hydrogels for vocal fold tissue engineering. *Journal of Voice*, 31(4):416-423, 2017.

[65] Thombare, N., Jha, U., Mishra, S., and Siddiqui, M. Z. Borax cross-linked guar gum hydrogels as potential adsorbents for water purification. *Carbohydrate Polymers*, 168:274-281, 2017.

[66] Abed, A., Assoul, N., Ba, M., Derkaoui, S. M., Portes, P., Louedec, L., and Meddahi-Pellé, A. Influence of polysaccharide composition on the biocompatibility of pullulan/dextran-based hydrogels. *Journal of Biomedical Materials Research Part A*, 96(3):535-542, 2011.

[67] Carvalho, J. M., Coimbra, M. A., and Gama, F. M. New dextrin-vinylacrylate hydrogel: Studies on protein diffusion and release. *Carbohydrate Polymers*, 75(2):322-327, 2009.

[68] Silva-Correia, J., Oliveira, J. M., Caridade, S. G., Oliveira, J. T., Sousa, R. A., Mano, J. F., and Reis, R. L. Gellan gum-based hydrogels for intervertebral disc tissue-engineering applications. *Journal of Tissue Engineering and Regenerative Medicine*, 5(6):e97-e107, 2011.

[69] Sennakesavan, G., Mostakhdemin, M., Dkhar, L. K., Seyfoddin, A., and Fatihhi, S. J. Acrylic acid/acrylamide based hydrogels and its properties-A review. *Polymer Degradation and Stability*, 180:109308, 2020.

[70] Sun, X. F., Liu, B., Jing, Z., and Wang, H. Preparation and adsorption property of xylan/poly (acrylic acid) magnetic nanocomposite hydrogel adsorbent. *Carbohydrate Polymers*, 118:16-23, 2015.

[71] Said, M., Atassi, Y., Tally, M., and Khatib, H. Environmentally friendly chitosan-g-poly (acrylic acid-co-acrylamide)/ground basalt superabsorbent composite for agricultural applications. *Journal of Polymers and the Environment*, 26(9):3937-3948, 2018.

[72] Ma, J., Zhou, G., Chu, L., Liu, Y., Liu, C., Luo, S., and Wei, Y. Efficient removal of heavy metal ions with an EDTA functionalized chitosan/polyacrylamide double network hydrogel. *ACS Sustainable Chemistry & Engineering*, 5(1):843-851, 2017.

[73] Panic, V. V., Madzarevic, Z. P., Volkov-Husovic, T., and Velickovic, S. J. Poly (methacrylic acid) based hydrogels as sorbents for removal of cationic dye basic yellow 28: Kinetics, equilibrium study and image analysis. *Chemical Engineering Journal*, 217:192-204, 2013.

[74] Xie, A. J., Yin, H. S., Liu, H. M., Zhu, C. Y., and Yang, Y. J. Chinese quince seed gum and poly (N, N-diethylacryl amide-co-methacrylic acid) based pH-sensitive hydrogel for use in drug delivery. *Carbohydrate Polymers*, 185:96-104, 2018.

[75] Akhmetzhan, A., Myrzakhmetova, N., Amangeldi, N., Kuanyshova, Z., Akimbayeva, N., Dosmaganbetova, S., and Longinos, S. N. A Short Review on the *N, N*-Dimethylacrylamide-Based Hydrogels. *Gels*, 7(4):234, 2021.

[76] Hernandez-Martínez, A. R., Lujan-Montelongo, J. A., Silva-Cuevas, C., Mota-Morales, J. D., Cortez-Valadez, M., de Jesus Ruíz-Baltazar, Á., and Herrera-Ordonez, J. Swelling and methylene blue adsorption of poly (N, N-dimethylacrylamide-co-2-hydroxyethyl methacrylate) hydrogel. *Reactive and Functional Polymers*, 122:75-84, 2018.

[77] KazemiAshtiani, M., Zandi, M., Shokrollahi, P., Ehsani, M., and Baharvand, H. Surface modification of poly (2-hydroxyethyl methacrylate) hydrogel for contact lens application. *Polymers for Advanced Technologies*, 29(4):1227-1233, 2018.

[78] Ranjha, N. M., Mudassir, J., and Akhtar, N. Methyl methacrylate-co-itaconic acid (MMA-co-IA) hydrogels for controlled drug delivery. *Journal of Sol-Gel Science and Technology*, 47(1):23-30, 2008.

[79] Çöle, G., Gök, M. K., and Güçlü, G. Removal of basic dye from aqueous solutions using a novel nanocomposite hydrogel: N-vinyl 2-pyrrolidone/itaconic acid/organo clay. *Water, Air, & Soil Pollution*, 224(11):1-16, 2013.

[80] Kaemmerer, E., Melchels, F. P., Holzapfel, B. M., Meckel, T., Hutmacher, D. W., and Loessner, D. Gelatine methacrylamide-based hydrogels: an alternative three-dimensional cancer cell culture system. *Acta biomaterialia*, 10(6):2551-2562, 2014.

[81] Tuncaboylu, D. C., Argun, A., Sahin, M., Sari, M., and Okay, O. Structure optimization of self-healing hydrogels formed via hydrophobic interactions. *Polymer*, 53(24):5513-5522, 2012.

[82] Bilici, C., Can, V., Nöchel, U., Behl, M., Lendlein, A., and Okay, O. Melt-processable shape-memory hydrogels with self-healing ability of high mechanical strength. *Macromolecules*, 49(19):7442-7449, 2016.

[83] Gajra, B., Pandya, S. S., Vidyasagar, G., Rabari, H., Dedania, R. R., and Rao, S. Poly vinyl alcohol hydrogel and its pharmaceutical and biomedical applications: A review. *International Journal of Pharmaceutical Research,* 4(2):20-26, 2012.

[84] Wang, Y., Huang, H., Wu, J., Han, L., Yang, Z., Jiang, Z., and Xu, M. Ultrafast self-healing, reusable, and conductive polysaccharide-based hydrogels for sensitive ionic sensors. *ACS Sustainable Chemistry & Engineering*, 8(50):18506-18518, 2020.

[85] Alexander, A., Khan, J., Saraf, S., and Saraf, S. Polyethylene glycol (PEG)–Poly (N-isopropylacrylamide)(PNIPAAm) based thermosensitive injectable hydrogels for biomedical applications. *European Journal of Pharmaceutics and Biopharmaceutics*, 88(3):575-585, 2014.

[86] Umar, A., Sanagi, M. M., Salisu, A., Ibrahim, W. A. W., Abd Karim, K. J., and Keyon, A. S. A. Preparation and characterization of starch grafted with methacrylamide using ammonium persulphate initiator. *Materials Letters*, 185:173-176, 2016.

[87] Nguyen, N. T. and Liu, J. H. Fabrication and characterization of poly (vinyl alcohol)/chitosan hydrogel thin films via UV irradiation. *European Polymer Journal*, 49(12): 4201-4211, 2013.

[88] Akala, E. O., Elekwachi, O., Chase, V., Johnson, H., Lazarre, M., and Scott, K. Organic redox-initiated polymerization process for the fabrication of hydrogels for colon-specific drug delivery. *Drug Development and Industrial Pharmacy*, 29(4):375-386, 2003.

[89] Akhtar, M. F., Ranjha, N. M., and Hanif, M. Effect of ethylene glycol dimethacrylate on swelling and on metformin hydrochloride release behavior of chemically crosslinked pH–sensitive acrylic acid–polyvinyl alcohol hydrogel. *DARU Journal of Pharmaceutical Sciences*, 23(1):1-10, 2015.

[90] Bao, Y., Ma, J., and Li, N. Synthesis and swelling behaviors of sodium carboxymethyl cellulose-g-poly (AA-co-AM-co-AMPS)/MMT superabsorbent hydrogel. *Carbohydrate Polymers*, 84(1):76-82, 2011.

[91] Zheng, Y. and Wang, A. Ag nanoparticle-entrapped hydrogel as promising material for catalytic reduction of organic dyes. *Journal of Materials Chemistry*, 22(32):16552-16559, 2012.

[92] Zerpa, A., Pakzad, L., and Fatehi, P. Hardwood kraft lignin-based hydrogels: production and performance. *ACS omega*, 3(7):8233-8242, 2018.

[93] Li, Y., Li, X., Zhou, L., Zhu, X., and Li, B. Study on the synthesis and application of salt-resisting polymeric hydrogels. *Polymers for Advanced Technologies*, 15(1-2):34-38, 2004.

[94] Athawale, V. D. and Vidyagauri, V. L. Graft copolymerization onto starch. 3: Grafting of acrylamide using ceric ion initiation and preparation of its hydrogels. *Starch-Stärke*, 50(10):426-431, 1998.

[95] Yazdani-Pedram, M., Retuert, J. and Quijada, R. Hydrogels based on modified chitosan, 1. Synthesis and swelling behavior of poly (acrylic acid) grafted chitosan. *Macromolecular Chemistry and Physics*, 201(9):923-930, 2000.

[96] Kabir, M. H., Ahmed, K., and Furukawa, H. The effect of cross-linker concentration on the physical properties of poly (dimethyl acrylamide-co-stearyl acrylate)-based shape memory hydrogels. *Microelectronic Engineering*, 150:43-46, 2016.

[97] Zainal, S. H., Mohd, N. H., Suhaili, N., Anuar, F. H., Lazim, A. M., and Othaman, R. Preparation of cellulose-based hydrogel: A review. *Journal of Materials Research and Technology*, 10:935-952, 2021.

[98] Pu, S., Ma, H., Zinchenko, A., and Chu, W. Novel highly porous magnetic hydrogel beads composed of chitosan and sodium citrate: an effective adsorbent for the removal of heavy metals from aqueous solutions. *Environmental Science and Pollution Research*, 24(19):16520-16530, 2017.

[99] Lim, D. J. Cross-Linking Agents for Electrospinning-Based Bone Tissu Engineering. *International Journal of Molecular Sciences*, 23(10):5444, 2022.

[100] Chang, C., Duan, B., Cai, J., and Zhang, L. Superabsorbent hydrogels based on cellulose for smart swelling and controllable delivery. *European Polymer Journal*, 46(1):92-100, 2010.

[101] Song, Y., Li, L., and Zheng, Q. Influence of epichlorohydrin modification on structure and properties of wheat gliadin films. *Journal of Agricultural and Food Chemistry*, 57(6):2295-2301, 2009.

[102] Vargas, G., Acevedo, J. L., López, J., and Romero, J. Study of cross-linking of gelatin by ethylene glycol diglycidyl ether. *Materials Letters*, 62(21-22):3656-3658, 2008.

[103] Bratskaya, S., Privar, Y., Nesterov, D., Modin, E., Kodess, M., Slobodyuk, A., and Pestov, A. Chitosan gels and cryogels cross-linked with diglycidyl ethers of ethylene glycol and polyethylene glycol in acidic media. *Biomacromolecules*, 20(4):1635-1643, 2019.

[104] Liu, C., Lei, F., Li, P., Wang, K., and Jiang, J. A review on preparations, properties, and applications of cis-ortho-hydroxyl polysaccharides hydrogels crosslinked with borax. *International Journal of Biological Macromolecules*, 182:1179-1191, 2021.

[105] Spoljaric, S., Salminen, A., Luong, N. D., and Seppälä, J. Stable, self-healing hydrogels from nanofibrillated cellulose, poly (vinyl alcohol) and borax via reversible crosslinking. *European Polymer Journal*, 56:105-117, 2014.

[106] Sharma, A. K., Kaith, B. S., and Arora, S. Synthesis of dextrin-polyacrylamide and boric acid based tough and transparent, self-healing, superabsorbent film. *International Journal of Biological Macromolecules*, 182:712-721, 2021.

[107] Gupta, N. V., and Shivakumar, H. G. Preparation and characterization of superporous hydrogels as gastroretentive drug delivery system for rosiglitazone maleate. *DARU Journal of Pharmaceutical Sciences*, 18(3):200, 2010.

[108] Pinho, E., Henriques, M., and Soares, G. Cyclodextrin/cellulose hydrogel with gallic acid to prevent wound infection. *Cellulose*, 21(6):4519-4530, 2014.

[109] Zaharia, A., Radu, A. L., Iancu, S., Florea, A. M., Sandu, T., Minca, I., and Iordache, T. V. Bacterial cellulose-poly (acrylic acid-co-N, N′-methylene-bis-acrylamide) interpenetrated networks for the controlled release of fertilizers. *RSC advances*, 8(32):17635-17644, 2018.

[110] Uliniuc, A., Hamaide, T., Popa, M., and Băcăiță, S. Modified starch-based hydrogels cross-linked with citric acid and their use as drug delivery systems for levofloxacin. *Soft Materials*, 11(4):483-493, 2013.

[111] Doshi, B., Ayati, A., Tanhaei, B., Repo, E., and Sillanpää, M. Partially carboxymethylated and partially cross-linked surface of chitosan versus the adsorptive removal of dyes and divalent metal ions. *Carbohydrate Polymers*, 197:586-597, 2018.

[112] Yu, Y., Xu, S., Li, S., and Pan, H. Genipin-cross-linked hydrogels based on biomaterials for drug delivery: a review. *Biomaterials Science*, 9(5):1583-1597, 2021.

[113] Yang, X., Wang, B., Sha, D., Liu, Y., Liu, Z., Shi, K., and Ji, X. PVA/poly (hexamethylene guanidine)/gallic acid composite hydrogel films and their antibacterial performance. *ACS Applied Polymer Materials*, 3(8):3867-3877, 2021.

[114] Hoffman, A. S. Hydrogels for biomedical applications. *Advanced Drug Delivery Reviews*, 64:18-23, 2012.

[115] Hoare, T. R., and Kohane, D. S. Hydrogels in drug delivery: Progress and challenges. *Polymer*, 49(8):1993-2007, 2008.

[116] Lalevée, G., David, L., Montembault, A., Blanchard, K., Meadows, J., Malaise, S., and Sudre, G. Highly stretchable hydrogels from complex coacervation of natural polyelectrolytes. *Soft Matter*, 13(37):6594-6605, 2017.

[117] Kuo, C. K., and Ma, P. X. Ionically crosslinked alginate hydrogels as scaffolds for tissue engineering: Part 1. Structure, gelation rate and mechanical properties. *Biomaterials*, 22(6):511-521, 2001.

[118] Le Tien, C., Lacroix, M., Ispas-Szabo, P., and Mateescu, M. A. N-acylated chitosan: hydrophobic matrices for controlled drug release. *Journal of Controlled Release*, 93(1):1-13, 2003.

[119] Zhang, H., Zhang, F., and Wu, J. Physically crosslinked hydrogels from polysaccharides prepared by freeze–thaw technique. *Reactive and Functional Polymers*, 73(7):923-928, 2013.

[120] Guan, Y., Bian, J., Peng, F., Zhang, X. M., and Sun, R. C. High strength of hemicelluloses based hydrogels by freeze/thaw technique. *Carbohydrate Polymers*, 101: 272-280, 2014.

[121] Ricciardi, R., Auriemma, F., De Rosa, C., and Lauprêtre, F. (2004). X-ray diffraction analysis of poly (vinyl alcohol) hydrogels, obtained by freezing and thawing techniques. *Macromolecules*, 37(5):1921-1927, 2004.

[122] He, G., Zheng, H., and Xiong, F. Preparation and swelling behavior of physically crosslinked hydrogels composed of poly (vinyl alcohol) and chitosan. *Journal of Wuhan University of Technology-Mater. Sci. Ed.*, 23(6):816-820, 2008.

[123] Sikdar, P., Uddin, M. M., Dip, T. M., Islam, S., Hoque, M. S., Dhar, A. K., and Wu, S. Recent advances in the synthesis of smart hydrogels. *Materials Advances*. 2(14): 4532-4573, 2021.

[124] Shin, B. M., Kim, J. H., and Chung, D. J. Synthesis of pH-responsive and adhesive super-absorbent hydrogel through bulk polymerization. *Macromolecular Research*, 21(5):582-587, 2013.

[125] Karadağ, E., Saraydın, D., and Güven, O. Radiation induced superabsorbent hydrogels. Acrylamide/itaconic acid copolymers. *Macromolecular Materials and Engineering*, 286(1):34-42, 2001.

[126] Ajji, Z., Mirjalili, G., Alkhatab, A., and Dada, H. Use of electron beam for the production of hydrogel dressings. *Radiation Physics and Chemistry*, 77(2):200-202, 2008.

[127] Athawale, V. D. and Lele, V. Graft copolymerization onto starch. II. Grafting of acrylic acid and preparation of its hydrogels. *Carbohydrate Polymers*, 35(1-2):21-27. 1998.

[128] Pourjavadi, A., Harzandi, A. M., and Hosseinzadeh, H. Modified carrageenan 3. Synthesis of a novel polysaccharide-based superabsorbent hydrogel via graft copolymerization of acrylic acid onto kappa-carrageenan in air. *European Polymer Journal*, 40(7):1363-1370, 2004.

[129] Demitri, C., Del Sole, R., Scalera, F., Sannino, A., Vasapollo, G., Maffezzoli, A., and Nicolais, L. Novel superabsorbent cellulose-based hydrogels crosslinked with citric acid. *Journal of Applied Polymer Science*, 110(4):2453-2460, 2008.

[130] Liu, Y., and Chan-Park, M. B. Hydrogel based on interpenetrating polymer networks of dextran and gelatin for vascular tissue engineering. *Biomaterials*, 30(2):196-207, 2009.

[131] Qu, J., Zhao, X., Ma, P. X., and Guo, B. pH-responsive self-healing injectable hydrogel based on N-carboxyethyl chitosan for hepatocellular carcinoma therapy. *Acta Biomaterialia*, 58:168-180, 2017.

[132] Mourdikoudis, S., Pallares, R. M., and Thanh, N. T. K. Characterization techniques for nanoparticles: comparison and complementarity upon studying nanoparticle properties. *Nanoscale*, 10(27):12871-12934, 2018.

[133] Geng, H. Preparation and characterization of cellulose/N, N'-methylene bisacrylamide/graphene oxide hybrid hydrogels and aerogels. *Carbohydrate Polymers*, 196:289-298, 2018.

[134] Hu, L., Zhang, P., Wang, X., Cheng, X., Qin, J., and Tang, R. pH-sensitive carboxymethyl chitosan hydrogels via acid-labile ortho ester linkage for potential biomedical applications. *Carbohydrate Polymers*, 178:166-179, 2017.

[135] Demirbilek, C., and Dinç, C. Ö. Synthesis of diethylaminoethyl dextran hydrogel and its heavy metal ion adsorption characteristics. *Carbohydrate Polymers*, 90(2):1159-1167, 2012.

[136] Thomas, M., Naikoo, G. A., Sheikh, M. U. D., Bano, M., and Khan, F. Effective photocatalytic degradation of Congo red dye using alginate/carboxymethyl cellulose/TiO_2 nanocomposite hydrogel under direct sunlight irradiation. *Journal of Photochemistry and Photobiology A: Chemistry*, 327:33-43, 2016.

[137] Fan, J., Shi, Z., Lian, M., Li, H., and Yin, J. Mechanically strong graphene oxide/sodium alginate/polyacrylamide nanocomposite hydrogel with improved dye adsorption capacity. *Journal of Materials Chemistry A*, 1(25):7433-7443, 2013.

[138] Tummalapalli, M. and Gupta, B. A UV-Vis spectrophotometric method for the estimation of aldehyde groups in periodate-oxidized polysaccharides using 2, 4-dinitrophenyl hydrazine. *Journal of Carbohydrate Chemistry*, 34(6):338-348, 2015.

[139] Sarma, D. D., Santra, P. K., Mukherjee, S., and Nag, A. X-ray photoelectron spectroscopy: a unique tool to determine the internal heterostructure of nanoparticles. *Chemistry of Materials*, 25(8):1222-1232, 2013.

[140] Zhang, M., Song, L., Jiang, H., Li, S., Shao, Y., Yang, J., and Li, J. Biomass based hydrogel as an adsorbent for the fast removal of heavy metal ions from aqueous solutions. *Journal of Materials Chemistry A*, 5(7):3434-3446, 2017.

[141] Yue, S., He, H., Li, B., and Hou, T. Hydrogel as a biomaterial for bone tissue engineering: A review. *Nanomaterials*, 10(8):1511, 2020.

[142] Vernon-Parry, K. D. Scanning electron microscopy: an introduction. *III-Vs Review*, 13(4):40-44, 2000.

[143] Vogel, V.,Schubert, D., and Kreuter, J. Comparison of scanning electron microscopy, dynamic light scattering and analytical ultracentrifugation for the sizing of poly(butyl cyanoacrylate) nanoparticles. *European Journal of Pharmaceutics and Biopharmaceutics*, 57(2):369-375, 2004.

[144] Karak, N. *Experimental Methods on Polymers, Nanomaterials and Their Nanocomposites*. Nova Science Publishers, New York, USA, 2016.

[145] Bhatia, M., Rajulapati, S. B., Sonawane, S., and Girdhar, A. Synthesis and implication of novel poly (acrylic acid)/nanosorbent embedded hydrogel composite for lead ion removal. *Scientific Reports*, 7(1):1-16, 2017.

[146] Djordjevic, I., Choudhury, N. R., Dutta, N. K., and Kumar, S. Synthesis and characterization of novel citric acid-based polyester elastomers. *Polymer*, 50(7):1682-1691, 2009.

[147] Rajisha, K. R., Deepa, B., Pothan, L. A., and Thomas, S. Thermomechanical and spectroscopic characterization of natural fibre composites. *Interface Engineering of Natural Fibre Composites for Maximum Performance*, 241-274, 2011.

[148] Singh, B., Sharma, D. K., and Gupta, A. Controlled release of thiram fungicide from starch-based hydrogels. *Journal of Environmental Science and Health, Part B*, 42(6):677-695, 2007.

[149] Mahmoud, G. A., Abdel-Aal, S. E., Badway, N. A., Abo Farha, S. A., and Alshafei, E. A. Radiation synthesis and characterization of starch-based hydrogels for removal of acid dye. *Starch-Stärke*, 66(3-4):400-408, 2014.

[150] Dai, J., Ma, S., Wu, Y., Han, L., Zhang, L., Zhua, J., and Liu, X. Polyesters derived from itaconic acid for the properties and bio-based content enhancement of soybean oil-based thermosets. *Green Chemistry*, 17(4):2383-2392, 2015.

[151] Singh, B., Varshney, L., and Francis, S. Designing tragacanth gum based sterile hydrogel by radiation method for use in drug delivery and wound dressing applications. *International Journal of Biological Macromolecules*, 88:586-602, 2016.

[152] ASTM D882-12, *Standard Test Method for Tensile Properties of Thin Plastic Sheeting*, ASTM International, West Conshohocken, PA, 2012.

[153] Gupta, K., Barua, S., Hazarika, S. N., Manhar, A. K., Nath, D., Karak, N., and Mandal, M. Green silver nanoparticles: enhanced antimicrobial and antibiofilm activity with effects on DNA replication and cell cytotoxicity. *RSC Advances*, 4(95):52845-52855, 2014.

[154] Balouiri, M., Sadiki, M., and Ibnsouda, S. K. Methods for in vitro evaluating antimicrobial activity: a review. *Journal of Pharmaceutical Analysis*, 6(2):71-79, 2016.

[155] Irshad, S., Mahmood, M., and Perveen, F. In-vitro anti-bacterial activities of three medicinal plants using agar well diffusion method. *Research Journal of Biology*, 02(01):1-8, 2012.

[156] Flory, P. J. Statistical mechanics of swelling of network structures. *The Journal of Chemical Physics*, 18(1):108-111, 1950.

[157] Wang, X., Zhang, Y., Hao, C., Dai, X., Zhu, F., and Ge, C. Ultrasonic synthesis and properties of a sodium lignosulfonate–grafted poly (acrylic acid-co-acryl amide) composite super absorbent polymer. *New Journal of Chemistry*, 38(12):6057-6063, 2014.

[158] El-Mohdy, H. A., Hegazy, E. S. A., and Abd El-Rehim, H. A. Characterization of starch/acrylic acid super-absorbent hydrogels prepared by ionizing radiation. *Journal of Macromolecular Science, Part A*, 43(7):1051-1063, 2006.

[159] Yan, Q., and Hoffman, A. S. Synthesis of macroporous hydrogels with rapid swelling and deswelling properties for delivery of macromolecules. *Polymer*, 36(4):887-889, 1995.

[160] Hu, X., Wei, W., Qi, X., Yu, H., Feng, L., Li, J., and Dong, W. Preparation and characterization of a novel pH-sensitive Salecan-g-poly (acrylic acid) hydrogel for controlled release of doxorubicin. *Journal of Materials Chemistry B*, 3(13):2685-2697, 2015.

[161] Du, H., Liu, M., Yang, X., and Zhai, G. The design of pH-sensitive chitosan-based formulations for gastrointestinal delivery. *Drug Discovery Today*, 20(8):1004-1011, 2015.

[162] Sung, H. W., Huang, D. M., Chang, W. H., Huang, R. N., and Hsu, J. C. Evaluation of gelatin hydrogel cross-linked with various cross-linking agents as bio-adhesives: in vitro study. *Journal of Biomedical Materials Research*, 46(4):520-530, 1999.

[163] Weber, L. M., Lopez, C. G., and Anseth, K. S. Effects of PEG hydrogel cross-linking density on protein diffusion and encapsulated islet survival and function. *Journal of Biomedical Materials Research*, 90(3):720-729, 2009.

[164] Qu, F., Zhang, Y., Rasooly, A., and Yang, M. Electrochemical biosensing platform using hydrogel prepared from ferrocene modified amino acid as highly efficient immobilization matrix. *Analytical Chemistry*, 86(2):973-976, 2014.

[165] Sun, X. F., Wang, H. H., Jing, Z. X., and Mohanathas, R. Hemicellulose-based pH-sensitive and biodegradable hydrogel for controlled drug delivery. *Carbohydrate Polymers*, 92(2):1357-1366, 2013.

[166] Zhu, J., Han, H., Ye, T. T., Li, F. X., Wang, X. L., Yu, J. Y., and Wu, D. Q. Biodegradable and pH sensitive peptide based hydrogel as controlled release system for antibacterial wound dressing application. *Molecules*, 23(12):3383, 2018.

[167] Liu, Y., Zhu, M., Liu, X., Zhang, W., Sun, B., Chen, Y., and Adler, H. J. P. High clay content nanocomposite hydrogels with surprising mechanical strength and interesting deswelling kinetics. *Polymer*, 47(1):1-5, 2006.

[168] Cui, W., Ji, J., Cai, Y. F., Li, H., and Ran, R. Robust, anti-fatigue, and self-healing graphene oxide/hydrophobically associated composite hydrogels and their use as recyclable adsorbents for dye wastewater treatment. *Journal of Materials Chemistry A*, 3(33):17445-17458, 2015.

[169] Guo, W., Lu, C. H., Orbach, R., Wang, F., Qi, X. J., Cecconello, A., and Willner, I. pH-Stimulated DNA hydrogels exhibiting shape-memory properties. *Advanced Materials*, 27(1):73-78, 2015.

[170] Shang, J., Le, X., Zhang, J., Chen, T., and Theato, P. Trends in polymeric shape memory hydrogels and hydrogel actuators. *Polymer Chemistry*, 10(9):1036-1055, 2019.

[171] Deng, Z., Wang, H., Ma, P. X., and Guo, B. Self-healing conductive hydrogels: preparation, properties and applications. *Nanoscale*, 12(3):1224-1246, 2020.

[172] Wang, W., Narain, R., and Zeng, H. Rational design of self-healing tough hydrogels: a mini review. *Frontiers in Chemistry*, 6:497, 2018.

[173] Aswathy, S. H., Narendrakumar, U., and Manjubala, I. Commercial hydrogels for biomedical applications. *Heliyon*, 6(4):e03719, 2020.

[174] Amin, M. C. I. M., Ahmad, N., Halib, N., and Ahmad, I. Synthesis and characterization of thermo-and pH-responsive bacterial cellulose/acrylic acid hydrogels for drug delivery. *Carbohydrate Polymers*, 88(2):465-473, 2012.

[175] Lin, F., Zheng, J., Guo, W., Zhu, Z., Wang, Z., Dong, B., and Lu, B. Smart cellulose-derived magnetic hydrogel with rapid swelling and deswelling properties for remotely controlled drug release. *Cellulose*, 26(11):6861-6877, 2019.

[176] Pina, S., Oliveira, J. M., and Reis, R. L. Natural-based nanocomposites for bone tissue engineering and regenerative medicine: a review. *Advanced Materials*, 27(7):1143-1169, 2015.

[177] Fan, C., Liao, L., Zhang, C., and Liu, L. A tough double network hydrogel for cartilage tissue engineering. *Journal of Materials Chemistry B*, 1(34):4251-4258, 2013.

[178] Nie, L., Deng, Y., Li, P., Hou, R., Shavandi, A., and Yang, S. Hydroxyethyl chitosan-reinforced polyvinyl alcohol/biphasic calcium phosphate hydrogels for bone regeneration. *ACS Omega*, 5(19):10948-10957, 2020.

[179] Tavakolian, M., Munguia-Lopez, J. G., Valiei, A., Islam, M. S., Kinsella, J. M., Tufenkji, N., and van de Ven, T. G. Highly absorbent antibacterial and biofilm-disrupting hydrogels from cellulose for wound dressing applications. *ACS Applied Materials & Interfaces*, 12(36):39991-40001, 2020.

[180] Das, A., Uppaluri, R., and Das, C. Feasibility of poly-vinyl alcohol/starch/glycerol/citric acid composite films for wound dressing applications. *International Journal of Biological Macromolecules*, 131:998-1007, 2019.

[181] Liang, Y., Zhao, X., Hu, T., Chen, B., Yin, Z., Ma, P. X., and Guo, B. Adhesive hemostatic conducting injectable composite hydrogels with sustained drug release and photothermal antibacterial activity to promote full-thickness skin regeneration during wound healing. *Small*, 15(12):1900046, 2019.

[182] Musgrave, C. S. A., and Fang, F. Contact lens materials: a materials science perspective. *Materials*, 12(2):261, 2019.