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Crosslinked natural hydrogels for drug delivery systems

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A B S T R A C T

Hydrogels made from a variety of materials may be used as a novel technology in regenerative medicine in the biomedical field. Hydrogels may be made using both chemical and physical processes, depending on the source material. Size, elastic modulus, swelling, and degradation rate are only a few of the many physical parameters that may be used to define hydrogels in experiments. Hydrogels made from natural polymers have been the focus of our review. Due to their remarkable biocompatibility and nontoxicity, simple gelation, and functionalization, hydrogels derived from natural polymers have received extensive attention in recent decades. As a result, natural polymer hydrogels are considered excellent biomaterials that have great potential in the biomedical field. Because carriers play such a large role in determining how far and how fast drugs reach their intended recipients, the need for intelligent drug delivery systems (DDSs) is on the rise. An outstanding goal of this study is to examine the impact that various crosslinking process parameters have on the drug delivery mechanism.

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1. Introduction

To induce a therapeutic effect, traditional drug administration sometimes requires repeated administration or large doses; this may reduce patient compliance and overall effectiveness, as well as cause significant toxicity and adverse effects [1-4]. Short circulation durations (less than 12 hours) and poor targeting and restrict oral administration, which is the most popular method for administration of drugs [5]. During the last several decades, researchers have focused on the development of drug carriers such as liposomes, nanoparticles, membranes, and hydrogels to address these difficulties [6, 7]. These drug delivery systems (DDSs) have the ability to regulate how drugs are delivered to tissues and cells throughout space and time. They may, in theory, increase the effectiveness of treatments while lowering their toxicity and dose requirements [7]. Various types of materials have been investigated in depth to determine their possible uses, with an emphasis on synthetic and natural materials [8-11]. Natural materials are preferable to artificial materials in terms of biocompatibility, accessibility, and ease of modification. Furthermore, different functional groups might be incorporated into the newly produced materials because of the reactive groups on the original natural materials, the freshly acquired materials are endowed with remarkable functions or their physical and chemical properties are altered [12, 13]. Furthermore, the natural materials might be combined with natural or other manufactured components to create hybrid materials [14-19].

There are several kinds of natural polymers, such as peptides, proteins, polysaccharides, etc., as often recognized. In terms of their process ability and biocompatibility, the first two classes of native polymers have been extensively studied in DDSs. Proteins and polysaccharide-based materials have more resemblance to the extracellular matrix, to provide less intrusive features for natural polymer-based DDSs [20, 21]. In addition, the backbones of polymers include several readily modifiable groups, including hydroxyl, carboxyl, and amino groups [22, 23]. More precise interactions between natural polymers and cells or organs have been discovered as a result of advances in life science research. Cellular activities, such as adhesion, migration, and proliferation, may be improved by using natural polymers with increased affinity for cell receptors. This presents a tremendous opportunity to design more targeted applications [23, 24].

Crosslinked water-soluble polymers are called hydrogels that are 3D networks. Hydrogels may be produced from almost any water-soluble polymer, including various chemical compositions and bulk physical properties [25]. Most hydrogels are composed of natural and synthetic polymers. Synthetic hydrogels are widely used nowadays because of their wide range of basic chemical resources, high water absorption, extended service life, and excellent process ability, synthetic hydrogels are extensively employed nowadays [26]. Nonetheless, excessive usage of synthetic hydrogels will impose enormous environmental and economic costs on civilization. In addition, it is difficult to ensure the toxicity and biocompatibility of synthetic hydrogels. Natural hydrogels are created from hydrophilic polymers obtained from nature, such as gelatin [27], alginate [28], starch [29], chitin [30], and cellulose [31]. These macromolecules are often derived from the biota of the earth. Consequently, judicious use of these resources may not only alleviate the issue of resource waste but also lessen the environmental damage and economic burden. Moreover, owing to their nontoxicity, biodegradability, biocompatibility, and sustainability, natural polymers are more appropriate for biomedical applications [32, 33].

As drug delivery vehicles, natural polymer hydrogels have gained significant interest [34-37]. Despite their effectiveness as drug carriers, existing hydrogel-based DDSs have drawbacks. The majority of pharmaceuticals, for instance, are released from porous hydrogels by passive processes such as molecular diffusion and hydrogel breakdown [38]. To increase the safety and efficacy of medication administration, controlled delivery hydrogels are in great demand [39]. In general, the bulk of these polymeric materials robs the matrix of its intended mechanical and degrading characteristics. Crosslinkers or crosslinking agents are the chemicals necessary to increase these qualities. Crosslinking is a straightforward way of modifying the degrading, biological, and mechanical characteristics of polymeric materials [40]. Physical or chemical linkages are formed between polymer chains. According to Martinez et al. [41], the selection of processing method and crosslinking approach has a substantial impact on every feature of protein-polymer films. The use of restricted, constant volume, and vapor phase crosslinking approaches decreased the equilibrium water content of protein polymers significantly. In particular, both restricted, vapor phase, and fixed volume methods affected drug delivery rates, with lower release rates and initial drug burst compared to crosslinking in the solution phase. Modifying the mechanical, physical, and drug release features of protein polymers is significantly facilitated by custom crosslinking techniques. In the study of Zhai et al. [42], three types of diselenide-rich polymers with unique hydrophobic side chains were manufactured. Dual drug-loaded crosslinked micelles were stable in healthy settings with low drug leakage and prolonged blood circulation, however, dual drug release was markedly increased in tumor redox microenvironments.

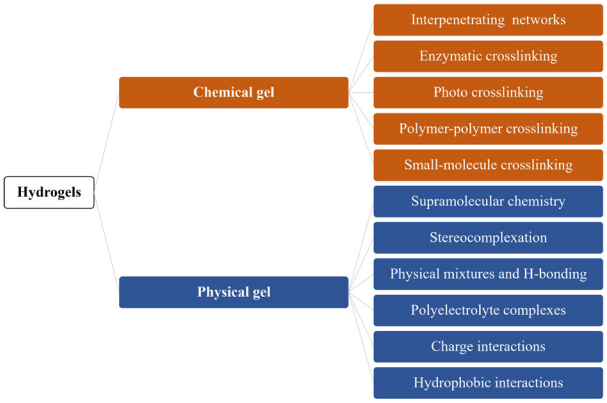

Fig. 1. Hydrogels classification according to crosslinking methods.

In DDSs, the amount and rate at which drugs reach their targets are strongly dependent on the carrier; hence, the need for intelligent DDSs is rising. However, there are some issues and challenges with how DDS can be performed and which variables need to be controlled more. The crosslinking of hydrogels is one of the major influential ways. The fundamental objective of this research is to examine the various kinds of crosslinked hydrogels as well as the influence of crosslinking process parameters on the drug delivery mechanism.

2. Crosslinking methods of natural hydrogels

Natural biopolymers such as alginate, chitosan, carrageenan, hyaluronan, and carboxymethyl cellulose (CMC) have been observed to form crosslinked networks [43, 44]. The different preparation processes employed include physical crosslinking [45], chemical crosslinking [46], grafting polymerization [47], and radiation crosslinking [48]. These adjustments may enhance the mechanical characteristics and viscoelasticity of materials used in pharmaceutical and biomedical applications [49]. The main procedures for creating chemical and physical gels (Fig. 1) are detailed here:

2.1. Chemically-crosslinked natural hydrogels

Hydrogels that have been chemically crosslinked facilitate the absorption of bioactive substances and/or water without dissolving and the diffusional release of drugs [50]. The chemical crosslinking technique utilizes covalent bonds between polymer chains to make persistent hydrogel [51]. The production of crosslinks was accomplished by the enzyme-catalyzed reaction, photosensitive agents, polymer-polymer conjugation, or the addition of small crosslinker molecules. The existence of functional groups (primarily OH, COOH, and NH_2), which may be employed to make hydrogels, is what gives water-soluble polymers their solubility. Covalent bonds between polymer chains may be produced by reacting functional groups with complementary reactivity, such as the isocyanate-OH/NH_2 reaction or the amine-carboxylic acid reaction, or by producing Schiff bases [45, 52].

2.1.1. Enzyme-catalyzed crosslinking

An enzyme-catalyzed crosslinking process between polymer chains is being used to generate in situ hydrogels. For this purpose, phosphatases, plasma amine oxidase, lysyl oxidase, phosphopantetheinyl transferase [53], tyrosinase [54], peroxidases [55], transglutaminases (TG) [56] are enzymes that were reported and investigated.

TG enzymes catalyze the production of very stable covalent connections between a protein's peptide-bound lysine or free amine group and its peptide-bound glutamine or g-carboxamide group [53]. Yung et al. [57] have created biocompatible and thermally stable gelatin hydrogels that are crosslinked by microbial TG (mTG) and can control the distribution of encapsulated regeneration cells (HEK293). Recombinant human TG (hTG) enzymes and animal-derived tissue TG (tTG) were utilized to crosslink two groups of protein polymers containing either glutamine or lysine completed crosslinking quicker than hTG (within 2 minutes) [56].

Soybean peroxidase and HRP are the commonly utilized peroxidase enzymes in the production of hydrogels. They enhance aniline conjugation and phenol derivatives in the H_2O_2 presence. In this process, HRP binds rapidly with H_2O_2 to produce a complex that may oxidize hydroxyphenyl groups in substances like tyramine and tyrosine [53]. Kim et al. [55] recently developed two-step HRP-catalyzed injectable tyramine-modified hyaluronic acid (HA-Tyr) hydrogels. In the first step, a bond of amide was formed among the carboxyl groups of HA and the amine groups of tyramine to form HA-Tyr conjugate. In the second step, HA-Tyr hydrogels were produced using a radical crosslinking process involving H_2O_2 and HRP. This hydrogel was utilized to provide intra-articular dexamethasone for rheumatoid arthritis therapy. By Jin et al. [58], the enzymatically crosslinked hydrogel was made from phloretic acid, chitosan-glycolic acid, and chitosan derivatives by utilizing HRP and H_2O_2 as crosslinking agents. This hydrogel has the potential for cartilage tissue engineering and can be created (gelation time) between 10 seconds and 4 minutes when the polymer concentration is between 3% and 1%.

The monophenol monooxygenase enzyme family includes tyrosinase, which is established in both plant and animal tissues. It has been utilized to crosslink gelatin and chitosan in situ to generate a hydrogel. The enzyme selectively oxidizes the tyrosyl residues of gelatin, creating reactive quinone residues, and the electron-rich amino groups of chitosan are covalently attached to the electron-poor quinone moiety, therefore forming intermolecular crosslinkages.

2.1.2. Photo crosslinking

The development of photo-crosslinked hydrogels is reliant based on photosensitive functional groups being present. When a photosensitive functional group is bonded to a polymer, it may create crosslinks when exposed to light, such as UV radiation [59]. Chitosan is one of these polymers that has been investigated more than others. A photo-crosslinkable chitosan hydrogel was produced by adding azide groups ($-N_3$) into the polymeric chain of chitosan. When exposed to UV light, the azide group is changed to the nitrene group (R-N:), which binds to the free amino groups of chitosan, resulting in the production of hydrogel in situ within one minute [60]. Between polymers, the photo-crosslinked hydrogel may also be created. UV irradiation was used to functionalize both polymers with photosensitive acrylate groups (CH_2=CHCOO) resulting in the thermosensitive chitosan-pluronic hydrogel. It was shown that the crosslinked polymer may release encapsulated human growth hormone (hGH) over an extended period when heated above the lower critical solution temperature (LCST) [61]. This combination was also used to transport plasmid DNA [62]. By altering chitosan with PEG and photoreactive azidobenzoic acid with argininylglycylaspartic acid peptide, a second chitosan-PEG hydrogel was created. Upon UV irradiation, a free-radical photo-initiated polymerization occurred, leading to the in situ synthesis of the hydrogel. The hydrogel resulted in improved distribution of cells and growth factors to the damaged myocardium [63].

This method has the benefit of facilitating the rapid and simple synthesis of the hydrogel. In contrast to chemical procedures, which often involve the inclusion of various reactive species, initiators, or catalysts, its manufacture is safe and inexpensive. This procedure, however, needs a photosensitizer and extended irradiation, which can also cause a local increase in temperature, so causing damage to nearby cells and tissue [64].

2.1.3. Hybrid polymer networks (HPN) or polymer-polymer crosslinking

Crosslinking take place among a polymeric chain's structural unit and another polymeric chain's structural unit in this hydrogel [65]. Thus, reactive functional groups must be pre-functionalized into polymers. Relying on the biodegradability of the resultant conjugates, choice of reactive functional groups, and required rate of crosslinking, many kinds of covalent bonds may be formed [66].

A well-studied in situ crosslinking process is the Michael addition between a nucleophile (such as a thiol or amine) and a vinyl group. Crosslinking of vinyl sulfone-functionalized dextrans with thiolated PEG is one example. The sort of strategy allows for the development of many types of quick production, biological inertness, and linkages of hydrogel [67]. The creation of a hydrazone bond between a hydrazide and an aldehyde enables the quick crosslinking of gel precursors [68].

2.1.4. Small-molecule crosslinking

Minimum requirements for the preparation of small-molecule crosslinking hydrogels are a small molecule crosslinker and one polymer in an acceptable solvent. In order to connect polymeric chains, crosslinkers, which have at least two reactive functional groups, are used [69]. There are two sorts of small crosslinkers: pharmacological molecules and bifunctional compounds. In the first scenario, the polymer and bi-functional molecule combine to entrap the drug molecule inside the hydrogel. In addition, drug molecules with two functional groups are covalently attached to polymeric chains to generate hydrogel without the need for crosslinkers. This method is only applicable to drugs with two reactive functional groups. Primaquine, a diamino drug, was recently used to crosslink periodate-oxidized gum arabic into a hydrogel by rapidly forming Schiff bases between the polymer's aldehyde and amine groups and the drug's amine groups [70].

Schiff base is the simple kind of crosslinking, occurring among amino and aldehyde groups. Using the Schiff reaction, dialdehydes such as glutaraldehyde and glyoxal [71] create covalent imine connections with the chitosan amino groups [72]. In other instances, HA-tyramine [73] and dextran-tyramine [71] were covalently bonded using hydrogen

peroxide (H_2O_2) and horseradish peroxidase (HRP) as crosslinkers to produce controllable gelation times hydrogels ranging from 5 seconds to nine minutes, depending on the reactant concentrations used. All of these small-molecule crosslinking techniques share the concern of the possible toxicity of unreacted crosslinker chemicals remaining in vivo. Glyoxal and Glutaraldehyde are known to be mutagenic and neurotoxic, respectively [72].

Genipin, a naturally occurring compound extracted from the fruit of the gardenia, is often used as a crosslinking agent in place of dialdehydes [58]. It has also been proven that genipin links polymers like gelatin and chitosan to biological tissues covalent. [74]. In addition, polymers containing amino-terminated groups, such as BSA [75], N, O-carboxymethyl chitosan, and PEG [76], crosslinked with genipin to produce hydrogels with varied dissolution rates ranging from 3 minutes to more than 100 days. Despite genipin's great biocompatibility, it is sensitive to interact with encapsulated drugs negatively, which is a disadvantageous related to gelation in the presence of treatment [66]. The current method was used to construct transdermal drug delivery for the controlled release of indomethacin, 5-fluorouracil, propranolol HCl, and oxprenolol HCl from gel beads [77].

2.1.5. Interpenetrating networks (IPNs)

A substance having two or more polymers in network form, where one polymer is crosslinked in the presence of another polymer is considered an IPN [78]. IPNs are called "alloys" of crosslinked polymers created without covalent connections between them [79]. Unless chemical links are disrupted, these networks cannot be separated [80]. At least one polymer must be crosslinked and/or generated in the presence of the other, both polymers must have comparable kinetics, and there must be no considerable phase separation among or between polymers [81]. An IPN is unique from other polymer combinations since it lacks viscoelasticity, swells but does not dissolve in any solvent, and lacks viscoelasticity [82]. IPN hydrogels are made from natural polymers and their derivatives, such as proteins and polysaccharides, as well as synthetic polymers with hydrophilic functional groups (e.g. -COOH, -OH, -$CONH_2$, SO_3H, amines, etc) [83].

Three polymers, such as poly (vinyl pyrrolidone) (PVP), PAA, and chitosan, and two crosslinking agents (such as N, N'-methylene-bisacrylamide, and glutaraldehyde) were used to create clarithromycin IPN hydrogels. The hydrogels produced by IPN have excellent mucoadhesion, allowing them to remain in the stomach's gastrointestinal environment for extended periods. Therefore, IPN hydrogel is utilized as a means of drug delivery for peptic ulcer treatment and H. pylori infection [84]. Semi-IPN hydrogels were produced by crosslinking a PVP and chitosan mixture with glutaraldehyde. The resulting semi-IPN gels were able to distribute clarithromycin in the stomach medium [85]. Kulkarni et al. [86] developed prazosin hydrochloride IPN hydrogel membranes for transdermal delivery using polyvinyl alcohol (PVA) and sodium alginate (SA) as polymers. The inclusion of crosslinker glutaraldehyde increased the film's rigidity, and the amount of glutaraldehyde in membranes determines the film's rigidity and in vitro drug release capabilities. IPN membranes extended the release of prazosin hydrochloride for up to 24 hours, while PVA and SA membranes alone resulted in fast drug release. The encapsulation efficiency reached 82 percent, and the drug release was sustained for up to 12 hours [87].

In comparison to single-network hydrogels, the swelling/deswelling response of multicomponent networks and mechanical strength, such as IPNs, are superior [88]. In addition, gel stiffness, hydrogel porosity, and crosslinking density may be tailored to the intended use in IPN-based hydrogels. Two major drawbacks are: (1) it is difficult to contain many different therapeutic agents, especially IPN and sensitive bimolecular agents, and (2) its preparation requires toxic agents such as crosslinkers, activators, and initiators to catalyze or initiate the polymerization and/or to catalyze or initiate the crosslinking or polymerization, respectively [89].

2.2. Physically-crosslinked natural hydrogels

Physical crosslinking may be accomplished by hydrogen bonds, chain complexion, polymer stereocomplexation, crystallization, chain aggregation, and hydrophobic association [90]. Due to the lack of harmful crosslinking agents, these hydrogels offer a wide variety of biological pharmacological applications. Due to the absence of a crosslinking agent, it is difficult to regulate the physical hydrogel's material characteristics, such as degradation time, chemical functionalization, network pore size, and gelation duration. In addition, this hinders the enhancement of mechanical properties [91, 92].

There are numerous methods for creating physically crosslinked hydrogels without the production of new covalent bonds, such as hydrophobic, ionic, electrostatic, and hydrogen bonding interactions between the building units [93]. Watanabe et al. [94] In the presence of potassium ions, they used the non-ionic polysaccharide dextran to make hydrogels. The researchers thought that the ionic radius of the potassium ion would fit into the cage made by the six oxygen atoms of the glucose units. However, the hydrogel they made was unstable in water. Reis et al. [95], for example, reported pH-responsive hydrogels based on modified gum arabic. 15 minutes of stirring an aqueous solution containing modified gum arabic with 0.1 mmol sodium persulfate, followed by 30 minutes of heating at 70 °C, produced a hydrogel. The hydrogel exhibited a significant pH dependence. For ionic interaction-induced hydrogel formation, the ionic groups presence on the polymer is not always necessary. Following is a list of the many ways documented for physical crosslinking:

2.2.1. Ionic bonding

Ionic bonding with polymers do not need the presence of ionic groups and may be crosslinked at ambient temperature and physiological pH. Alginate, which contains glucuronic and mannuronic acid residues and may be crosslinked with ions of calcium, is a noteworthy example. These gels are used as a matrix for the encapsulation and release of proteins from live cells. In a similar fashion, hydrogels are created by crosslinking chitosan with glycerol-phosphate disodium salt. Chitosan solutions containing this salt stay liquid at room temperature but rapidly convert into a gel upon heating. These gels may facilitate the active protein-induced production of cartilage and bone. Carrageenan, a polysaccharide composed of 1,4-linked—D-galactose and 1,3-linked—D-galactose with an uneven proportion of sulfate groups, gels with potassium ions, or in the absence of salt. In the metallic ions presence, it is possible to build stronger hydrogels [96-99]. In the potassium ions' presence, dextran is another natural polymer that produces hydrogels. Due to the gel's inability to withstand water, it is less suitable for administering drugs [45].

2.2.2. Stereocomplex formation

This approach produces physically crosslinked hydrogels for DDSs by forming stereocomplexes between polymers with opposing chirality. The creation of these hydrogels is facilitated by each component dissolving in water and combining the resulting solution. However, only a few polymer compositions are used for such structures. Dextran hydrogels physically crosslinked via the stereocomplex production of lactic acid oligomers are examples of such systems. However, 11 lactic acid units were needed for hydrogel formation in the grafts [100]. The protein was suspended in dextran-g-oligolactate solutions prior to the mixing stage. Under physiological conditions, the gels were found to be completely degraded. The period of degradation was determined by the

hydrogel's composition, specifically the number of initial water content, lactate grafts, and the length and polydispersity of those grafts [101].

2.2.3. Crystallization

Crystallization, which includes repeated freezing and thawing, may produce a gel that is both robust and very elastic. Such a development was initially observed in synthetic hydrogel poly (vinyl alcohol) (PVA) hydrogels. These are now widely used in biotechnology sectors, particularly in the production of peptides and proteins. There are uses for PVA/gelatin, PVA/starch, and PVA/chitosan hydrogels made by freeze-thawing in tissue engineering [96]. Crystallization may also be used to make dextran microspheres and hydrogels. An increase in the concentration of low molecular weight dextran was observed after the addition of salts and stirring. Precipitates dissolve rapidly in dimethyl sulfoxide or boiling water while being insoluble in water at a normal temperature [102].

Crystallization was used by Stenekes et al. [103] to produce dextran hydrogel microspheres. Dextran 6000 of low molecular weight was precipitated from a concentrated aqueous solution. The rate of precipitation accelerated with increasing dextran solution concentration. The precipitation process was increased by the presence of salts and agitation. Differential scanning calorimetry confirmed the crystalline nature of the precipitates. Researchers hypothesized that hydrogen bonds between polymer chains and water in highly concentrated dextran solutions induced crystallization.

2.2.4. Hydrophobized polysaccharides

By hydrophobic modification, polysaccharides such as carboxymethyl curdlan, pullulan, dextran, and chitosan may be physically crosslinked. Such hydrogels with crosslinking have potential in DDSs. The palmitoyl-substituted hydrophobized water-soluble glycol chitosan is hemocompatible, biocompatible, and capable of entrapping water-soluble pharmaceuticals [104].

In the Mihajlovic et al. [105] study, the composition of the hydrogel was hydrophilic PEG and hydrophobic dimer fatty acid. Self-assembly of fatty acids in a micellar microstructure led to the formation of the hydrogel network. At equilibrium swelling, the resulting hydrogels comprised between 75% and 92% by weight of water and exhibited good mechanical characteristics. An anisotropic lamellar hydrogel was made by Haque et al. [106] by stacking a bilayered structure of polymerizable surfactant (dodecyl glyceryl itaconate) that was hydrophobically associated within a polyacrylamide matrix that was hydrophilic.

2.2.5. Electrostatic

Hydrogel formation may also originate from electrostatic interactions between polyelectrolytes. Charged groups on biopolymers may engage in electrostatic interactions with one another or with other charged species in solution [107]. Gotoh et al. [108] produced chitosan-alginate hybrid gel beads for Cd(II), Co(II), and Cu(II) adsorption from a wastewater stream based on electrostatic interaction between amino groups on chitosan and carboxyl groups on alginic acid. On the hydrogel based on electrostatic forces, adsorption was reported to be dramatically accelerated. This finding demonstrated the capability of the beads to absorb heavy metal ions from wastewater. pH-sensitive hydrogels have been created by Huang et al. [109] using the strong electrostatic interaction between anionic groups in polyacrylic acid (PAA) and cationic guar gum (CG). The researchers studied the hydrogel matrix's ability to release ketoprofen. At pH 7.4, there was no diffusion of ketoprofen, but at more basic pH values, the drug was observed to be transported.

2.2.6. Hydrogen bonding

An electron-deficient hydrogen atom may be linked to a functional group with high electron density through a hydrogen bond to help in the formation of hydrogels in gelatin-based hydrogels. The temperature of the solution, the kind of solvent, the concentration of the polymer, and the molar ratio of each polymer are only a few of the aspects that must be addressed in this sort of physical crosslinking [45]. Crosslinked injectable hydrogel structures can be made with natural polymers like gelatin-agar, starch-carboxymethyl cellulose, and HA-MC [110].

The types of crosslinked natural hydrogels, their polymer systems, and the drugs they contain are listed in Table 1.

3. Drug delivery potentials

In recent decades, several studies have been performed on biomaterials composed of polysaccharides and proteins. The biological polymers derived from diverse plant and animal sources include gallan, dextran, starch, and chitosan. In recent years, these biopolymers have gained a variety of benefits, as researchers continue to develop and examine these biomaterials to meet the demanding requirements of biomedical applications in drug administration. Numerous polysaccharide and protein-based polymeric networks, such as guar gum, konjac glucomannan, and dextran containing acrylic acid, have been fabricated [147]. Methods of crosslinking synthesis enable the functionalization of medicines and other therapeutic agents for the development of novel DDSs [148]. The hydrogel design discusses meshes and crosslinked polymers that permit the loading and diffusion of complex solutions. When functionalizing, care must be given to the mesh size [149]. At the beginning of the hydrogel synthesis, this approach may be used with the drug in combination with the other reagents, or it can be used at the end after the hydrogel has been formed [150]. In situ loading is appropriate for hydrophilic medicines and consists of dissolving the drug and polymer powder in water. The alternative procedure, known as post-loading, involves the prolonged immersion of dried hydrogel sheets in a drug solution. After drug inclusion, the hydrogel has a dry state and provides protection in both instances. In addition, crosslinkers are crucial for the regulated release of medicinal drugs with a low or high molecular weight, and degradable crosslinkers are preferable [151]. Table 2 discusses several natural polymers utilized for DDSs and their characteristics.

Natural polysaccharides may be used to create remarkable localized hydrogel release systems by modifying the physical-chemical characteristics and manufacturing process described in the preceding sections. Natural polysaccharides share similarities with the extracellular matrix (ECM), possess optimal bio properties, and have great cellular connections [155]. These properties allow the use of natural polysaccharides at targeted target areas as porous 3D matrices, in situ hydrogels, and/or microspheres. Consequently, the localized administration of polysaccharide drug systems is a crucial aspect of many medical procedures and processes, including transdermal applications, GI tract abnormalities, tissue healing, cancer treatment, and others. The polysaccharide may contain growth factors and entire cells for improved disease therapy and wound healing, in addition to incorporating diverse medicinal compounds into hydrogel DDSs.

3.1. Drug–hydrogel interactions

Before injection into the body, hydrogels used for DDSs are typically manufactured outside of the body and infused with pharmaceuticals. There are a variety of crosslinking processes available, including chemical and UV photo-polymerization crosslinking procedures. These crosslinking methods are only useful if all harmful chemicals can be removed before the hydrogel is implanted, which may be challenging without also leaking drug-loaded hydrogel. Since bulk hydrogels have a defined dimensionality and often a high elasticity, it is generally not

practical to extrude them using a needle. Occasionally, this issue may be overcome by transforming the prepared gel into nano- or microparticles. Hydrogels may be produced in situ (i.e. in vivo) for certain purposes, however, the risks of UV irradiation (and the need for additional equipment) or crosslinking chemicals must be taken into account [50].

On the other hand, the DDS could be a linear polymer that is not crosslinked. The viscosity of a linear polymer matrix is often related to the rate at which a drug is released from it [156]. Nonetheless, it may be challenging or impossible to dissolve the polymer(s) of interest in sufficient concentration to provide the desired degree of control over the rate of drug release. Even if this were possible, the yield stress of the resulting material might be so high that it can't be injected, or its viscosity might be so high that it can't flow through a long and/or narrow extrusion device (needle, laparoscope), as Poiseuille's equation says. Another reason why crosslinking is so important is because water-soluble polymer chains that aren't crosslinked disintegrate and expand within hours after entering the body's water. For these reasons, formulations that have the characteristics of linear polymer solutions outside the body (allowing for simple injection) but gel in situ inside the body (thereby allowing for extended drug release profiles) have attracted a large amount of attention and funding. Several chemical and physical crosslinking methods have been used to bring about in situ gelation. [50].

3.2. Gel network engineering

In order to control the drugs diffusion from hydrogel matrices, a

Table 1.
Composition and drug incorporation of various natural hydrogel forms.

Drug Type	Crosslinking method	Sort of polymers	References
Clarithromycin	Interpenetrating networks	PVP, PAA and Chitosan	[111]
Clarithromycin		PVP and Chitosan	[112]
Prazosin HCl		PVA and sodium alginate	[87]
Theophylline		methylcellulose and chitosan	[113]
5-fluorouracil		PX and chitosan	[114]
Regenerative cells (HEK293)	Enzymatic crosslinking	Gelatin crosslinked by mTG	[115]
Interleukin-2		Gelatin crosslinked by mTG	[116]
Dexamethasone		Tyramine modified HA by HRP	[117]
Cells and growth factors	Photo crosslinking	Modified PEG-chitosan	[118]
Human growth hormone (hGH)		Pluronic-chitosan	[119]
Plasmid DNA		Modified PEG-chitosan	[120]
Bone morphogenetic protein-2	Polymer-polymer crosslinking	HA with aldehyde or amino functionality	[121]
Budesonide and tissue plasminogen activator		Crosslinked HA	[122]
Growth factor and bone precursor cells		Adipic acid dihydrazide and poly(aldehyde guluronate)	[123]
Primaquine	Small-molecule	Oxidized gum arabic	[124]
Oxprenolol HCl		Genipin	[125]
BSA		Genipin	[126]
5-Fluorouracil		Chitosan	[127]
Propanolol HCl		Chitosan	[128]
Indomethacin		Alginate–chitosan	[77]
---	Supramolecular chemistry	PPO-grafted dextran & β-cyclodextrin	[129]
---	Stereocomplexation	D-lactide oligomers and Dextran precursors grafted L-lactide	[130]
Metronidazole	Physical mixtures and H-bonding	PVA and Carboxymethyl tamarind kernel polysaccharide	[131]
Gentamycin and Minocycline		PVA and chitosan	[132, 133]
Metoprolol tartrate		PVA and Carboxymethyl tamarind kernel polysaccharide	[134]
----	Polyelectrolyte complexes	PAA and quaternized chitosan	[135]
Dexamethasone		Polyanionic N-carboxymethyl chitosan and polycationic N-trimethyl chitosan	[136]
Osteoblasts		Chitosan and phosphorylated chitosan (a polycation)	[137]
----		Chitosan and alginate	[138]
----		Poly-(γ-glutamic acid) (γ-PGA) and chitosan	[139]
----		Chitosan and gelatin	[140]
Metoprolol tartrate		k-carrageenan, carboxymethyl cellulose sodium, and chitosan with sodium alginate	[141]
BSA	Hydrophobic interactions	Alginate solution	[142]
BSA		Chitosan grafted with PEG 40	[143]
5-fluorouracil and Riboflavin		PNIPAM grafted with HA and chitosan	[144]
Meloxicam		PX 407, Chitosan and Carbopol-934	[145]
Doxorubicin HCl	Charge interactions	HTCC and GP	[146]

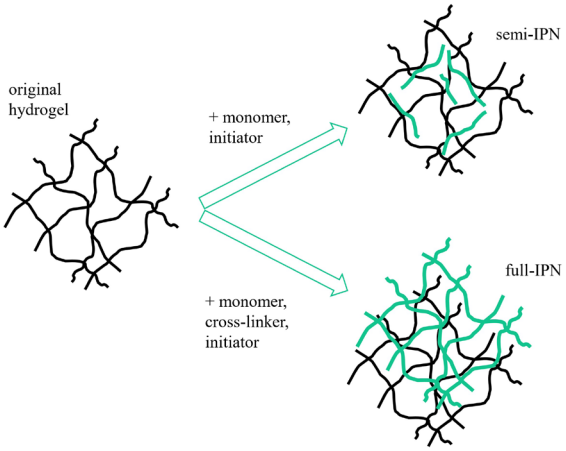

Fig. 2. Full- and semi-IPN structure and formation.

variety of methods have been tested, including altering the microstructure of the hydrogel network or the hydrogel surface [157]. It has also been shown that permanent covalent networks are established owing to polymer crosslinking, resulting in higher mechanical strength of the polymers which may be attributed to the free flow of water/bioactive molecules. The principal uses of covalently crosslinked chitosan are in site-specific sustained drug administration by diffusion, and as permanent networks utilized in tissue engineering [158]. Increasing the proportion of crosslinking monomer added into the gel is a straightforward approach for achieving these alterations. Nevertheless, heavily crosslinked gels display relatively sluggish reactions to environmental stimuli and may possess poor mechanical characteristics. Consequently, it may be necessary to use more advanced tactics.

The surface morphology and bulk stability are enhanced by the interlocking structure of crosslinked IPN components. By using IPN creation, comparatively dense hydrogel matrices with more robust mechanical characteristics and stiffer may be manufactured. IPN hydrogels are more effective for drug delivery than ordinary hydrogels [159]. A complete IPN may be produced using a crosslinker, as shown in Fig. 2, or a network of embedded linear polymers entrapped inside the original hydrogel can be created without a crosslinker, as shown in Fig. 2. (semi-IPN). IPNs may be used to create thick hydrogel matrices with more strong mechanical features and stiffer, more widely regulated physical attributes, and (typically) more efficient drug loading. Polymerization of the interpenetrating hydrogel phase and drug loading often occur concurrently [160].

IPN surface chemistries and pore sizes can also be modified to customize drug release kinetics, hydrogel-tissue interactions, and mechanical gel properties [161]. Swelling responses to physiological situations can be controlled by using interpenetrating phases with various degradation profiles or varied swelling responses to physiological conditions [162]. IPNs can limit how environmental changes affect hydrogel responses and burst drug release by controlling the equilibrium swelling of one or both interpenetrating phases based on the elasticity (crosslinking density) of one or both gel phases. Such a network, which includes both a pH-sensitive hydrogel and a hydrolyzable hydrogel, inhibits a pH-swelling hydrogel's generally fast swelling reaction to allow for linear swelling profiles after a sudden drop in pH from 7.4 to 2 [163]. For oral DDS, this responsiveness is perfect for reducing burst drug release. Chitosan–PNIPAM interpenetrating networks considerably enhanced the loading capacity of diclofenac compared to PNIPAM hydrogels with no crosslinking [164], while maintaining the considerable thermosensitivity of the PNIPAM phase to regulate the release kinetics.

Semi-IPNs may be better able to maintain quick kinetic reaction rates to temperature or pH because of the lack of a restricted interpenetrating elastic network, while still providing the majority of the advantages of IPNs in DDS (e.g. slowing drug release, pore size modification, etc.). Reversible pH switching of theophylline release is achieved by embedding theophylline-binding polyallylammonium chloride in hydrogels made from acrylamide/acrylic acid copolymers [165].

3.3. Biorthogonal methods

In biomedical applications, in situ-forming hydrogels are preferred over premade hydrogels due to the fact that gelation may occur under physiological conditions upon injection, reducing the need for surgical operations. The precursor polymer solution's initial fluidity promotes optimal shape adaption, and biological components may be included into the hydrogel by simply mixing the precursor polymer solution with the biological components [166, 167]. Physical crosslinks, such as hydrophobic or ionic contacts, may occur in situ under moderate circumstances, although the resultant hydrogels often dissolve or deteriorate quickly. By photo-curing polymers functionalized with vinylic groups, injectable hydrogels with chemical crosslinking have been produced regularly [146]. Although the presence of photo-initiators and polymerization radicals has been associated to cytotoxicity, cells encapsulated in this kind of hydrogel are often compatible with cells [168, 169]. However, significant disadvantages of photo-crosslinkable devices include UV radiation's limited penetrability and its potentially harmful effects on live tissue. In situ production of hydrogels through covalent crosslinking of polymers with complementary functional groups has garnered significant attention during the last two decades. The production of Schiff bases between amines and aldehydes [170] and the Ugi and Passerini condensation are early examples of chemical crosslinking reactions that generate hydrogels [171]. Because of this, hydrogels cannot be used as in situ-forming DDSs because they may react with biomolecule functional groups such as proteins [172].

Bioorthogonal, chemoselective crosslinking approaches that do not interfere with biological processes or biomolecules are very desired in this setting. Click chemistry, commonly known as the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of terminal alkynes and azides, is the most extensively researched chemoselective crosslinking method for hydrogels. Sharpless et al. [172] used this term to characterize an assortment of new regiospecific linking reactions with high yields and often minimal purification needs. The Hilborn group reported the first PVA-

Table 2.
Natural hydrogels as DDSs.

Hydrogels	DDS potential	References
Xylan	Antioxidant and anticancer qualities suppress cell mutation, difficult to digest in the humans intestines and stomach.	[152]
Chitosan	Enhances medication paracellular transport, pain relief, stimulates intestinal adsorption, antimicrobial characteristics, antihypertension, promotion of hemostasis, antiulcer, epidermal cell development, cholesterol reduction	[153]
Cellulose	Diabetic foot ulcer treatment using a topical gel, Controlled drug release (for colon-specific and oral DDS)	[154]
Guar gum	Controlled drug release (for colon-specific and oral DDS)	[153]
Dextran	Drug delivery in the colon	[153]
Collagen	For spinal fusion, bone fracture repair, and oral maxillofacial reconstruction	[154]

based, click-chemistry-crosslinked hydrogel [173]. In addition to tissue engineering, this hydrogel class has been used to regulate the release of drugs and other biomolecules, such as pDNA [174], bovine serum albumin (BSA) [175], and doxorubicin [176]. Due to the necessity for a copper catalyst in "traditional" alkyne–azide cyclosynthesis, strain-promoted azide-alkyne cycloadditions (SPAAC) are becoming more popular. Cyclooctyne groups' intrinsic ring strain facilitates rapid and effective crosslinking without the need for catalysts or external stimuli such as UV light in this reaction For the treatment of excessive post-operative bone growth, Hermann et al. [177] showed the injection of bone morphogenetic protein (BMP) inhibitors using PEG hydrogels in children who had surgery to repair early fusion of the sutures (craniosynostosis). Poly [(tetraethylene glycol methacrylate)-co-(azidotetraethylene glycol methacrylate)] and a 4-dibenzocyclooctynol PEG crosslinker, as indicated by oscillatory rheology, created hydrogels within 30 seconds of mixing. In vitro release studies indicated that the BMP inhibitor Gremlin1 remained effective after being dissolved in prepolymer solutions and then incorporated into hydrogels, confirming the bioorthogonal nature of the SPAAC crosslinking method. When the prepolymer solutions were injected with Gremlin1 into a surgically produced brain injury in weanling mice, a hydrogel capable of releasing the inhibitor for 14 days grew in situ. Using this method, scientists were able to limit postoperative bone regeneration in a model with a cranial lesion, but not completely prevent it. Resynostosis therapy's ultimate objective is to temporarily block the formation of bone after surgery, but then let the bone regenerate as the child ages, the current technique has the potential to be used as a treatment for craniosynostosis after surgical intervention. In addition to thiol–ene/yne reactions [178], native chemical ligation [179], oxime chemistry [180], and Diels–Alder cycloadditions are promising bioorthogonal techniques for the synthesis of chemically crosslinked hydrogels [181].

4. Controlled release mechanisms

After loading the drug into a hydrogel, it may be released in a variety of ways, including environmental-responsive, chemically-controlled, swelling-controlled, and diffusion-controlled [182].

To achieve the optimal drug release rate, a hydrogel's drug characteristics and beginning concentration must be taken into consideration together with its intended use and the kind of ailment that is being treated [183]. For successful drug distribution and release, a hydrogel with appropriate characteristics has to be created based on the above-mentioned dependencies. Preferably, altering the average pore size allows the drug release rate to be controlled (mesh size). The crosslinking density in the gel network may be used to modify the hydrogel's high porosity structure. Pore size decreases with increasing crosslinking density and vice versa. By adding crosslinker (chemical or physical crosslinking approach) or by using various other techniques (e.g. UV polymerization), it is possible to improve the crosslinking density [104]. pH and temperature, as well as changes in polymer concentration, may all affect mesh size [184]. It is possible to modify the rate of drug release by changing the mesh size, which alters the diffusion pathways of the drug molecules [185].

Mathematical modeling may also be used to enhance the design of hydrogels that can be used to regulate the release of drugs. In systems like this, where diffusion is the primary mode of mass transfer, determining the drug diffusion coefficient is critical [186]. Pores, tiny crevices between macromolecular chains, allow drug molecules to diffuse. Pore size is often determined by the length of correlation (ε), which is the distance between neighboring crosslinks. Diffusion distances between macromolecular chains may be measured using this unit of measurement. One of the most critical structural metrics for describing the hydrogel network's structure is the correlation length [187]. The mesh size of the hydrogel is often referred to as. It is possible that this classification is erroneous, however, the correlation length and thus the predicted mesh size are lowered in the case of hydrogels with higher crosslinker addition. So it may be hypothesized that correlation length directly influences hydrogel network mesh size [186]. Drug release from hydrogel may be accomplished by various methods including swelling/deswelling/diffusion and chemical processes. It is described major mechanisms of drug release especially influenced by crosslinking parameters as below:

4.1. Diffusion

The ability to immobilize active substances and biomolecules by crosslinking aids in controlled drug release. To alter macroscopic features like Young's modulus and diffusion, crosslinking density is widely employed to alter important parameters like molecular weight and mesh size between crosslinkers. It is critical for the health of live cells in biological systems that tiny molecules, such as nutrients, diffuse freely [188]. A popular method for drug release from hydrogels is passive diffusion, which allows for the free diffusion in and out during the loading and storage of a wide range of molecules [189].

As previously mentioned, hydrogels are 3D, crosslinked polymeric networks that expand when exposed to water. The network structure of the hydrogel is governed by the crosslink, which may be either chemical (covalent bonding) or physical (hydrogen bonding, electrostatic interactions, and hydrophobic contacts). The hydrogel's mesh size is a measure of the number of open spaces in the hydrogel network. Because it is affected by crosslinker and polymer concentrations as well as environmental stimuli, hydrogel mesh size affects how drug diffuse across the hydrogel network. As a consequence of the network abnormalities and polymer polydispersity caused by the gelation of hydrogels by polymerization, the mesh size is often heterogeneous [154].

For large-mesh drug release ($r_{mesh}/r_{drug} > 1$), diffusion takes over the mechanism of drug release. The diffusion of small drug molecules is essentially unaffected by the network mesh size. The Stokes-Einstein equation Eq. (1) [190] states that the diffusivity, D, is proportional to the radius of the drug molecule (r_{drug}) and the solution's viscosity (η):

$$D = \frac{RT}{6\pi\eta r_{drug}} \quad \text{Eq. (1)}$$

where T is the absolute temperature and R is the gas constant.

Steric hindrance becomes an issue when the mesh size is near to the drug size ($r_{mesh}/r_{drug} \approx 1$) Finally, significant steric hindrance immobilizes drugs and keeps them physically entrapped within the network until the network degrades or the mesh size grows, for example, in response to external stimuli, for very tiny mesh sizes and/or very big drug molecules ($r_{mesh}/r_{drug} < 1$) [182].

Another method of managing the release of active molecules from physical hydrogels is to create them to degrade spontaneously under physiological settings [191]. Enzyme activity [192] and hydrolysis [193] are the most common mechanisms for degradation. Water-soluble hydrogels may degrade on the surface or in bulk, removing or eroding polymer mass. There are several hydrogels available that may be manipulated to achieve desired release rates ranging from weeks to months by changing the surface and bulk erosion. When the rate of diffusion of these agents is faster than the rate of bond disintegration, bulk erosion occurs due to permeability to degrading enzymes or water. In contrast, surface erosion occurs when link breakdown occurs at a faster pace than water or enzyme penetration into the gel bulk [194].

Fick's first rule of diffusion states that hydrogel drug release is primarily controlled by diffusion (with variable or constant diffusion coefficients). The diffusion of a drug through a hydrogel matrix is up to

the mesh sizes inside the gel matrix, which are impacted by a variety of variables, including external stimuli, the contributing monomers chemical structure, and the crosslinking degree within the gel matrix. When it comes to the physical qualities of a hydrogel network, the mesh size has a significant impact on its degradability and mechanical strength. When swelled, biomedical hydrogel mesh diameters may be in the range of 5–100 nm, which is substantially bigger than the average molecular size of a typical small-molecule drug. Therefore, drug diffusion is not significantly slowed in hydrogels, but macromolecules with hydrodynamic radii, such as peptides, oligonucleotides, and proteins, will have sustained release unless the mesh size and structure are optimized for macromolecular diffusion [195].

The membrane's hydrophilicity altered with pH and temperature. However, the crosslinking density of membranes would also affect the rate of penetration. With increasing crosslinking density, the intramolecular space would shrink, resulting in decreased fertilizer penetration. Zhang et al. [196] developed a cellulose film co-crosslinked with PVA for ammonium salt release. The ammonium salt penetration rate decreased as crosslinker concentration increased. In general, the coating is regarded to be the most suitable form for fertilizers. Large fertilizer usage necessitates a high loading content, which is one of the most advantageous properties of permeation-type CRF. Using toluene diisocyanate as a crosslinker for urea coating, Qiu et al. [197] created a cellulose membrane. With increasing crosslinking density, the urea penetration rate was drastically reduced due to the increased hydrophobicity and decreased free volume percentage.

4.2. Chemically-controlled release

The gel matrix's chemical reactions govern the release under chemical control [198]. They include enzymatic or hydrolytic degradation of polymeric chains, as well as interactions between the polymer network and the releasing drug that are either non-reversible or reversible [199]. In addition to the above indicated release mechanisms, two additional processes have been identified as impacting drug release rate: hydrogel bulk or surface erosion or the binding equilibrium among the drug binding moieties incorporated into hydrogels [200]. The degradation events taking place in the delivery matrix determine the release of the medicine in chemically controlled systems. Polymer degradation (bond cleavage) is the rate-determining process for drug release in the pendant chain, and diffusion is expected to be low. One of the most prevalent types is the pendant chain. The other is the EDR system, where polymer degradation and drug diffusion occur at the same time. To accurately forecast the release of the medicine, both elements must be taken into account. When it comes to synthetic hydrogel systems, erodible systems are especially intriguing. Drug release rates are not influenced by diffusion in any of these chemically controlled systems [201].

Crosslinkers unite molecules, increase molecular weight, and typically give greater mechanical characteristics and increased stability. However, crosslinking also leads to poorer degradability, lesser availability of functional groups in the crosslinked polymer, and affects the rheology of the polymers, leading to future processing challenges and the probable increase in cytotoxicity [202].

Network degradation may also be used to control the release of medicinal molecules from a hydrogel. As the hydrogel network degrades, the mesh size expands, enabling medicines to escape [203]. Backbone and crosslinks can be degraded by hydrolysis or the action of enzymes. It is possible to alter the transport properties of bioactive chemical release strategies by altering the handles used. Bio-responsive domains can be introduced to the polymer network to provide cell-responsive actions [204].

For the regulated release of bioactive siRNA, biodegradable hydrogels can also be employed [205]. Using a gelatin hydrogel, Saito et al.

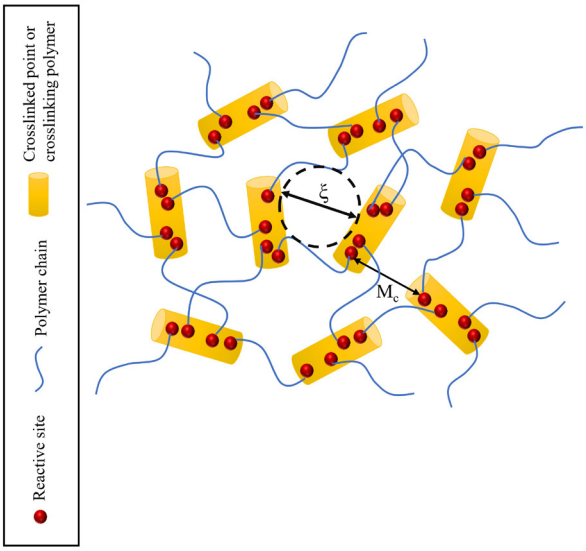

Fig. 3. Illustration of a hydrogel consisting of hydrophilic polymer chains joined by crosslink sites or crosslinking polymers.

[206] were able to regulate the release of siRNA. Cationized gelatin (CG) was combined with siRNA in the various ratio of amino groups of gelatin to phosphate groups of siRNA in order to produce the siRNA-CG nanocomplex. The siRNA was released and inhibited gene expression once the siRNA-CG hydrogel was broken down. Hydrogels may not only release siRNA, but they may also retain their bioactivity for a long amount of time, as demonstrated by this study. Endogenous angiogenesis and osteogenesis were boosted by the prolonged administration of the miR-26a enhancer.

4.3. Swelling

Understanding the varied processes involved in drug release from swellable polymer matrices is vital in order to the rational design of DDSs that correspond to the required temporal and spatial drug release schedules to satisfy the various therapeutic demands [207].

According to Gibas and Janik [208], hydrogel swelling is a complicated event involving many phases of water absorption processes that do not entail the disintegration of the polymer network. The swelling of biomaterials in aqueous settings is mediated by the hydrophilicity of the polymer network resulting from the polar group's presence (such as–SO_3H, –COOH, –NH_2, and –OH). In addition to osmotic pressure gradients and capillary effects, osmotic pressure gradients and capillary effects are additional important processes of water entry into the 3D network of the hydrogel. The fact that the hydrogel network structure's interconnections keep the material stable despite the fact that the crosslinked junctions' rubber elastic pressures offset the effect of solubility is fascinating [90]. When a drug's diffusion rate is substantially faster than the hydrogel's distention rate, swelling is thought to influence release behavior in the swelling-controlled mechanism [209]. Optimal design and characterization of hydrogel scaffold degradation, bioactive chemical diffusion, and cell migration across the hydrogel network may be achieved by controlling the hydrogel network structure [12,22]. When determining the hydrogel's network structure, researchers looked at four key swelling characteristics:

- The expansion ratio (Q), comprises the volume expansion ratio (Q_v) and the ratio of mass expansion (Q_m)
- The volume fraction of the polymer in the state of swollen (υ2,s).
- The number of average molecular weight crosslinks per molecule (Mc)
- The size of the network mesh (ξ) (Fig. 3).

κCarrageenan hydrogel and beta-carotene were used as the drug and

the device in a model system for controlled drug release by Hezaveh and colleagues [210]. Using the dripping method, different concentrations of genipin were used to crosslink the beta-carotene-containing beads. Results reveal that the swelling ratio of crosslinked beads decreases when genipin concentration rises under all pH conditions (pH 7.4 and pH 1.2). An examination of the network's microstructure demonstrates that crosslinking has enhanced its structure and stability. When beads are crosslinked, the diffusion coefficient for the release of encapsulated beta-carotene demonstrates a reduced diffusivity. As shown by models of swelling based on adaptive neural fuzzy logic, the use of genipin as a crosslinker in κC/NaCMC alters the mechanism of transport. Using glutaraldehyde as the crosslinking agent, a variety of crosslinked LVCS/PVA hydrogels with different feed contents were synthesized in the study by Khan and Ranjha [147]. The swelling of hydrogels reduced as the crosslinking ratio increased, as the hydrogel structure became more compact. It was discovered that when glutaraldehyde concentration rose, porosity reduced and gel fraction increased. As the ratio of crosslinking agent rose in the hydrogel structure, drug release reduced due to the strong physical entanglements between polymers.

5. Future direction

New techniques for crosslinking, one of the useful features of hydrogels, have improved the efficacy of these materials. Innovative crosslinking techniques, which are regarded as an influential influence on the characteristics of hydrogels, have contributed to the enhancement of these materials' performance. Extensive advances over the past 50 years have transformed relatively simple networks of hydrogels into complex multi components systems. Because of easy administration and simple combination of active agents, in situ forming hydrogels is expected to have an effective role as controlled DDSs.

Therefore, the usage of hydrogels that gel both physically and chemically in tandem that able to combine injectability with mechanical strength is an excellent method. While localized and controlled diffusion is facilitated in the detection of a cellular event by enzyme response systems, Multi-responder hydrogels allow more control over the release of stimulated drug in response to environmental stimuli. With the advent of bio-inks and the enhancement of additive manufacturing, increasingly, 3D-printed hydrogels mimic the complex functional and biological architecture of natural tissues.

The improvement of cellular control and behavior by the combination and release of active substances, like 3D-printed growth factors, may represent a significant advance in tissue engineering. In contrast to macroscopic hydrogels, nanogels are administered intravenously and transport medications to the cell during therapeutic administration. Notable is the targeting of triggered medication delivery in response to intracellular signals. The effect of microgels and nanogels on increasing the local transport of drug molecules and amphiphilic nanogels in the delivery of proteins and peptides are examples of progress in this field. These innovations create enhanced, more efficient, and individualized controlled DDSs that promote medication targeting and DDS therapy.

Although several challenges to the development of this viewpoint remain unsolved, it is considered that new ideas are useful in enhancing the safety, efficiency, and application of hydrogels, and their function in DDS has been emphasized:

1. Polymers with the desired functional groups that are hydrophilic
2. multiarm / multifunctional structures, like star polymers and branching or grafted co-polymers, which in the future would provide superior characteristics and be suitable for a broader variety of possible uses.

6. Conclusions

This review studied the natural hydrogels applicability for controlled drug delivery. Chemical and physical interactions may alter the physical and chemical characteristics of hydrogels. These interactions provide a suitable platform for the emergence of many applications in DDS, especially natural hydrogels with respect to controlled local drug delivery. Over the last five decades, hydrogels have undergone an evolution from simple physically or chemically crosslinked networks to complex multi-component systems. Today's hydrogels which are able to releasing controlled and triggered therapies have also an effective role as controlled DDSs with features such as easy administration and simple combination of active agents. Unlike conventional hydrogels with the capability of prolonged single component release, Today's ones provide controlled and triggered release of multiple therapeutics in a spatial and temporal manner.

REFERENCES

[1] W.B. Liechty, D.R. Kryscio, B.V. Slaughter, N.A. Peppas, Polymers for drug delivery systems, Annual review of chemical and biomolecular engineering 1 (2010) 149-173.
[2] M. Alizadeh, M. Paydar, F.S. Jazi, Structural evaluation and mechanical properties of nanostructured Al/B_4C composite fabricated by ARB process, Composites Part B: Engineering 44(1) (2013) 339-343.
[3] F. Sharifianjazi, A.J. Rad, A. Esmaeilkhanian, F. Niazvand, A. Bakhtiari, L. Bazli, M. Abniki, M. Irani, A. Moghanian, Biosensors and nanotechnology for cancer diagnosis (lung and bronchus, breast, prostate, and colon): A systematic review, Biomedical Materials (2021).
[4] V.P.S. Sidhu, R. Borges, M. Yusuf, S. Mahmoudi, S.F. Ghorbani, M. Hosseinikia, P. Salahshour, F. Sadeghi, M. Arefian, A comprehensive review of bioactive glass: synthesis, ion substitution, application, challenges, and future perspectives, Journal of Composites and Compounds 3(9) (2021) 247-261.
[5] M.S. Alqahtani, M. Kazi, M.A. Alsenaidy, M.Z. Ahmad, Advances in oral drug delivery, Frontiers in Pharmacology 12 (2021) 618411.
[6] M.W. Tibbitt, J.E. Dahlman, R. Langer, Emerging frontiers in drug delivery, Journal of the American Chemical Society 138(3) (2016) 704-717.
[7] G. Tiwari, R. Tiwari, B. Sriwastawa, L. Bhati, S. Pandey, P. Pandey, S.K. Bannerjee, Drug delivery systems: An updated review, International journal of pharmaceutical investigation 2(1) (2012) 2.
[8] D.F.A. Loghin, G. Biliuta, S. Coseri, E.S. Dragan, Preparation and characterization of oxidized starch/poly (N, N-dimethylaminoethyl methacrylate) semi-IPN cryogels and in vitro controlled release evaluation of indomethacin, International journal of biological macromolecules 96 (2017) 589-599.
[9] M. Farokhi, F. Mottaghitalab, M.A. Shokrgozar, K.-L. Ou, C. Mao, H. Hosseinkhani, Importance of dual delivery systems for bone tissue engineering, Journal of Controlled Release 225 (2016) 152-169.
[10] Z. Goudarzi, N. Parvin, F. Sharifianjazi, Formation of hydroxyapatite on surface of SiO_2–P_2O_5–CaO–SrO–ZnO bioactive glass synthesized through sol-gel route, Ceramics International 45(15) (2019) 19323-19330.
[11] F. Sharifianjazi, P. Zeydi, M. Bazli, A. Esmaeilkhanian, R. Rahmani, L. Bazli, S. Khaksar, Fibre-Reinforced Polymer Reinforced Concrete Members under Elevated Temperatures: A Review on Structural Performance, Polymers 14(3) (2022) 472.
[12] X. Qi, L. Lin, L. Shen, Z. Li, T. Qin, Y. Qian, X. Wu, X. Wei, Q. Gong, J. Shen, Efficient decontamination of lead ions from wastewater by salecan polysaccharide-based hydrogels, ACS Sustainable Chemistry & Engineering 7(12) (2019) 11014-11023.
[13] X. Qi, W. Wei, J. Li, Y. Liu, X. Hu, J. Zhang, L. Bi, W. Dong, Fabrication and characterization of a novel anticancer drug delivery system: salecan/poly (methacrylic acid) semi-interpenetrating polymer network hydrogel, ACS Biomaterials Science & Engineering 1(12) (2015) 1287-1299.
[14] X. Qi, W. Wei, J. Li, T. Su, X. Pan, G. Zuo, J. Zhang, W. Dong, Design of Salecan-containing semi-IPN hydrogel for amoxicillin delivery, Materials Science and Engineering: C 75 (2017) 487-494.
[15] E.S. Dragan, A.I. Cocarta, Smart macroporous IPN hydrogels responsive to pH, temperature, and ionic strength: synthesis, characterization, and evaluation of controlled release of drugs, ACS applied materials & interfaces 8(19) (2016)

12018-12030.
[16] M.M. Lazar, I.A. Dinu, M. Silion, E.S. Dragan, M.V. Dinu, Could the porous chitosan-based composite materials have a chance to a "NEW LIFE" after Cu (II) ion binding?, International journal of biological macromolecules 131 (2019) 134-146.
[17] E.S. Dragan, D. Humelnicu, M.V. Dinu, Development of chitosan-poly (ethyleneimine) based double network cryogels and their application as superadsorbents for phosphate, Carbohydrate polymers 210 (2019) 17-25.
[18] E.S. Dragan, D. Humelnicu, M.V. Dinu, R.I. Olariu, Kinetics, equilibrium modeling, and thermodynamics on removal of Cr (VI) ions from aqueous solution using novel composites with strong base anion exchanger microspheres embedded into chitosan/poly (vinyl amine) cryogels, Chemical Engineering Journal 330 (2017) 675-691.
[19] F. Sharifianjazi, S. Khaksar, A. Esmaeilkhanian, L. Bazli, S. Eskandarinezhad, P. Salahshour, F. Sadeghi, S. Rostamnia, S.M. Vahdat, Advancements in Fabrication and Application of Chitosan Composites in Implants and Dentistry: A Review, Biomolecules 12(2) (2022) 155.
[20] F. Sharifianjazi, A. Esmaeilkhanian, M. Moradi, A. Pakseresht, M.S. Asl, H. Karimi-Maleh, H.W. Jang, M. Shokouhimehr, R.S. Varma, Biocompatibility and mechanical properties of pigeon bone waste extracted natural nano-hydroxyapatite for bone tissue engineering, Materials Science and Engineering: B 264 (2021) 114950.
[21] R. Alisani, N. Rakhshani, M. Abolhallaj, F. Motevalli, P.G.-s. Abadi, M. Akrami, M. Shahrousvand, F.S. Jazi, M. Irani, Adsorption, and controlled release of doxorubicin from cellulose acetate/polyurethane/multi-walled carbon nanotubes composite nanofibers, Nanotechnology 33(15) (2022) 155102.
[22] X. Qi, Y. Yuan, J. Zhang, J.W. Bulte, W. Dong, Oral administration of salecan-based hydrogels for controlled insulin delivery, Journal of agricultural and food chemistry 66(40) (2018) 10479-10489.
[23] J. Chen, J. Ouyang, Q. Chen, C. Deng, F. Meng, J. Zhang, R. Cheng, Q. Lan, Z. Zhong, EGFR and CD44 dual-targeted multifunctional hyaluronic acid nanogels boost protein delivery to ovarian and breast cancers in vitro and in vivo, ACS applied materials & interfaces 9(28) (2017) 24140-24147.
[24] F.S. Rezaei, F. Sharifianjazi, A. Esmaeilkhanian, E. Salehi, Chitosan films and scaffolds for regenerative medicine applications: A review, Carbohydrate polymers 273 (2021) 118631.
[25] T. RAO, P. CHVS, Hydrogels the three dimensional networks: a review, Int J Curr Pharm Res 13(1) (2021) 12-17.
[26] F. Wang, Y. Zhang, Y. Wang, Recycling of Waste Cotton Sheets into Three-Dimensional Biodegradable Carriers for Removal of Methylene Blue, ACS omega 6(50) (2021) 34314-34326.
[27] Y. Fang, N. Qiao, H. Deng, M. Ren, Y. Zhang, D. Zhang, H. Lin, Y. Chen, K.T. Yong, J. Xiong, PEDOT: PSS-Based Microfluidic-Spun Microfibers for Tunable Release of Acetaminophen via Electrical Stimulation, Advanced Materials Technologies 2200103.
[28] V. Manish, K.V. Siva, A. Arockiarajan, G. Tamadapu, Synthesis and characterization of hard magnetic soft hydrogels, Materials Letters (2022) 132323.
[29] H. Lu, X. Li, H. Yang, J. Wu, Y. Zhang, H. Huang, Preparation and properties of riboflavin-loaded sanxan microcapsules, Food Hydrocolloids 129 (2022) 107641.
[30] M.J. Monteiro, M.F. Cunningham, Polymer Colloids: Synthesis Fundamentals to Applications, ACS Publications, 2020, pp. 4377-4378.
[31] J. Lu, Y. Li, H. Zhu, G. Shi, SiO_2-Coated Fe_3O_4 Nanoparticle/Polyacrylonitrile Beads for One-Step Lipase Immobilization, ACS Applied Nano Materials 4(8) (2021) 7856-7869.
[32] D.M. Nascimento, Y.L. Nunes, M.C. Figueirêdo, H.M. de Azeredo, F.A. Aouada, J.P. Feitosa, M.F. Rosa, A. Dufresne, Nanocellulose nanocomposite hydrogels: technological and environmental issues, Green Chemistry 20(11) (2018) 2428-2448.
[33] F. Sharifianjazi, M. Irani, A. Esmaeilkhanian, L. Bazli, M.S. Asl, H.W. Jang, S.Y. Kim, S. Ramakrishna, M. Shokouhimehr, R.S. Varma, Polymer incorporated magnetic nanoparticles: Applications for magnetoresponsive targeted drug delivery, Materials Science and Engineering: B 272 (2021) 115358.
[34] H.N. Abdelhamid, A.P. Mathew, Cellulose-Based Nanomaterials Advance Biomedicine: A Review, International Journal of Molecular Sciences 23(10) (2022) 5405.
[35] J. Liao, B. Hou, H. Huang, Preparation, properties and drug controlled release of chitin-based hydrogels: An updated review, Carbohydrate Polymers (2022) 119177.
[36] L. Lei, Y. Bai, X. Qin, J. Liu, W. Huang, Q. Lv, Current Understanding of Hydrogel for Drug Release and Tissue Engineering, Gels 8(5) (2022) 301.
[37] B. Fu, H.-C. Lin, N. Chen, P. Zhao, Adenosine triphosphate/pH dual-responsive controlled drug release system with high cancer/normal cell selectivity and low side toxicity, Journal of Biomaterials Applications (2022) 08853282221087412.
[38] A. Bordbar-Khiabani, M. Gasik, Smart Hydrogels for Advanced Drug Delivery Systems, International Journal of Molecular Sciences 23(7) (2022) 3665.
[39] E.R. Aluri, E. Gannon, K. Singh, S. Kolagatla, K. Kowiorski, S. Shingte, E. McKiernan, C. Moloney, K. McGarry, L. Jowett, Graphene oxide modulates inter-particle interactions in 3D printable soft nanocomposite hydrogels restoring magnetic hyperthermia responses, Journal of Colloid and Interface Science 611 (2022) 533-544.
[40] N. Reddy, R. Reddy, Q. Jiang, Crosslinking biopolymers for biomedical applications, Trends in biotechnology 33(6) (2015) 362-369.
[41] A.W. Martinez, J.M. Caves, S. Ravi, W. Li, E.L. Chaikof, Effects of crosslinking on the mechanical properties, drug release and cytocompatibility of protein polymers, Acta biomaterialia 10(1) (2014) 26-33.
[42] S. Zhai, X. Hu, Y. Hu, B. Wu, D. Xing, Visible light-induced crosslinking and physiological stabilization of diselenide-rich nanoparticles for redox-responsive drug release and combination chemotherapy, Biomaterials 121 (2017) 41-54.
[43] M. Radmansouri, E. Bahmani, E. Sarikhani, K. Rahmani, F. Sharifianjazi, M. Irani, Doxorubicin hydrochloride-Loaded electrospun chitosan/cobalt ferrite/titanium oxide nanofibers for hyperthermic tumor cell treatment and controlled drug release, International journal of biological macromolecules 116 (2018) 378-384.
[44] P. Abasian, M. Radmansouri, M.H. Jouybari, M.V. Ghasemi, A. Mohammadi, M. Irani, F.S. Jazi, Incorporation of magnetic NaX zeolite/DOX into the PLA/chitosan nanofibers for sustained release of doxorubicin against carcinoma cells death in vitro, International journal of biological macromolecules 121 (2019) 398-406.
[45] W.E. Hennink, C.F. van Nostrum, Novel crosslinking methods to design hydrogels, Advanced drug delivery reviews 64 (2012) 223-236.
[46] M. Ermis, S. Calamak, G.C. Kocal, S. Guven, N.G. Durmus, I. Rizvi, T. Hasan, N. Hasirci, V. Hasirci, U. Demirci, Hydrogels as a new platform to recapitulate the tumor microenvironment, Handbook of nanomaterials for cancer theranostics, Elsevier2018, pp. 463-494.
[47] Y. Su, T. Feng, W. Feng, Y. Pei, Z. Li, J. Huo, C. Xie, X. Qu, P. Li, W. Huang, Mussel-inspired, surface-attachable initiator for grafting of antimicrobial and antifouling hydrogels, Macromolecular Rapid Communications 40(17) (2019) 1900268.
[48] P. Liu, M. Zhai, J. Li, J. Peng, J. Wu, Radiation preparation and swelling behavior of sodium carboxymethyl cellulose hydrogels, Radiation Physics and Chemistry 63(3-6) (2002) 525-528.
[49] Y.-C. Nho, J.-H. Lee, Reduction of postsurgical adhesion formation with hydrogels synthesized by radiation, Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms 236(1-4) (2005) 277-282.
[50] T.R. Hoare, D.S. Kohane, Hydrogels in drug delivery: Progress and challenges, polymer 49(8) (2008) 1993-2007.
[51] Z. Ahmad, S. Salman, S.A. Khan, A. Amin, Z.U. Rahman, Y.O. Al-Ghamdi, K. Akhtar, E.M. Bakhsh, S.B. Khan, Versatility of Hydrogels: From Synthetic Strategies, Classification, and Properties to Biomedical Applications, Gels 8(3) (2022) 167.
[52] M.S.N. Shahrbabak, F. Sharifianjazi, D. Rahban, A. Salimi, A comparative investigation on bioactivity and antibacterial properties of sol-gel derived 58S bioactive glass substituted by Ag and Zn, Silicon 11(6) (2019) 2741-2751.
[53] L.S.M. Teixeira, J. Feijen, C.A. van Blitterswijk, P.J. Dijkstra, M. Karperien, Enzyme-catalyzed crosslinkable hydrogels: emerging strategies for tissue engineering, Biomaterials 33(5) (2012) 1281-1290.
[54] S.-H. Kim, S.-H. Lee, J.-E. Lee, S.J. Park, K. Kim, I.S. Kim, Y.-S. Lee, N.S. Hwang, B.-G. Kim, Tissue adhesive, rapid forming, and sprayable ECM hydrogel via recombinant tyrosinase crosslinking, Biomaterials 178 (2018) 401-412.
[55] K. Kim, S. Park, J.-A. Yang, J.-H. Jeon, S. Bhang, B.-S. Kim, S. Hahn, Injectable hyaluronic acid–tyramine hydrogels for the treatment of rheumatoid arthritis, Acta biomaterialia 7(2) (2011) 666-674.
[56] N.E. Davis, S. Ding, R.E. Forster, D.M. Pinkas, A.E. Barron, Modular enzymatically crosslinked protein polymer hydrogels for in situ gelation, Biomaterials 31(28) (2010) 7288-7297.
[57] C. Yung, L. Wu, J. Tullman, G. Payne, W. Bentley, T. Barbari, Transglutaminase crosslinked gelatin as a tissue engineering scaffold, Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 83(4) (2007) 1039-1046.
[58] R. Jin, L.M. Teixeira, P.J. Dijkstra, M. Karperien, C. Van Blitterswijk, Z. Zhong, J. Feijen, Injectable chitosan-based hydrogels for cartilage tissue engineering, Biomaterials 30(13) (2009) 2544-2551.
[59] H. Samadian, H. Maleki, Z. Allahyari, M. Jaymand, Natural polymers-based

light-induced hydrogels: Promising biomaterials for biomedical applications, Coordination Chemistry Reviews 420 (2020) 213432.
[60] B. Li, L. Wang, F. Xu, X. Gang, U. Demirci, D. Wei, Y. Li, Y. Feng, D. Jia, Y. Zhou, Hydrosoluble, UV-crosslinkable and injectable chitosan for patterned cell-laden microgel and rapid transdermal curing hydrogel in vivo, Acta biomaterialia 22 (2015) 59-69.
[61] H.S. Yoo, Photo-cross-linkable and thermo-responsive hydrogels containing chitosan and Pluronic for sustained release of human growth hormone (hGH), Journal of Biomaterials Science, Polymer Edition 18(11) (2007) 1429-1441.
[62] J. Im Lee, H.S. Kim, H.S. Yoo, DNA nanogels composed of chitosan and Pluronic with thermo-sensitive and photo-crosslinking properties, International journal of pharmaceutics 373(1-2) (2009) 93-99.
[63] Y. Yeo, W. Geng, T. Ito, D.S. Kohane, J.A. Burdick, M. Radisic, Photocrosslinkable hydrogel for myocyte cell culture and injection, Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 81(2) (2007) 312-322.
[64] J. Łukaszczyk, M. Śmiga, K. Jaszcz, H.J.P. Adler, E. Jähne, M. Kaczmarek, Evaluation of oligo (ethylene glycol) dimethacrylates effects on the properties of new biodegradable bone cement compositions, Macromolecular bioscience 5(1) (2005) 64-69.
[65] C.Y. Anthony, A.A. Smith, E.A. Appel, Structural considerations for physical hydrogels based on polymer–nanoparticle interactions, Molecular Systems Design & Engineering 5(1) (2020) 401-407.
[66] N. Bhattarai, J. Gunn, M. Zhang, Chitosan-based hydrogels for controlled, localized drug delivery, Advanced drug delivery reviews 62(1) (2010) 83-99.
[67] C. Hiemstra, L.J. van der Aa, Z. Zhong, P.J. Dijkstra, J. Feijen, Novel in situ forming, degradable dextran hydrogels by Michael addition chemistry: synthesis, rheology, and degradation, Macromolecules 40(4) (2007) 1165-1173.
[68] V.G. Muir, T.H. Qazi, S. Weintraub, B.O. Torres Maldonado, P.E. Arratia, J.A. Burdick, Sticking Together: Injectable Granular Hydrogels with Increased Functionality via Dynamic Covalent Inter-Particle Crosslinking, Small (2022) 2201115.
[69] J. Berger, M. Reist, J.M. Mayer, O. Felt, N. Peppas, R. Gurny, Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications, European journal of pharmaceutics and biopharmaceutics 57(1) (2004) 19-34.
[70] K. Nishi, A. Jayakrishnan, Self-gelling primaquine− gum arabic conjugate: an injectable controlled delivery system for primaquine, Biomacromolecules 8(1) (2007) 84-90.
[71] H.-F. Liang, M.-H. Hong, R.-M. Ho, C.-K. Chung, Y.-H. Lin, C.-H. Chen, H.-W. Sung, Novel method using a temperature-sensitive polymer (methylcellulose) to thermally gel aqueous alginate as a pH-sensitive hydrogel, Biomacromolecules 5(5) (2004) 1917-1925.
[72] W.S. Shim, J.-H. Kim, K. Kim, Y.-S. Kim, R.-W. Park, I.-S. Kim, I.C. Kwon, D.S. Lee, pH-and temperature-sensitive, injectable, biodegradable block copolymer hydrogels as carriers for paclitaxel, International journal of pharmaceutics 331(1) (2007) 11-18.
[73] M. Kurisawa, J.E. Chung, Y.Y. Yang, S.J. Gao, H. Uyama, Injectable biodegradable hydrogels composed of hyaluronic acid–tyramine conjugates for drug delivery and tissue engineering, Chemical communications (34) (2005) 4312-4314.
[74] H.W. Sung, I.L. Liang, C.N. Chen, R.N. Huang, H.F. Liang, Stability of a biological tissue fixed with a naturally occurring crosslinking agent (genipin), Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 55(4) (2001) 538-546.
[75] M.F. Butler, Y.F. Ng, P.D. Pudney, Mechanism and kinetics of the crosslinking reaction between biopolymers containing primary amine groups and genipin, Journal of Polymer Science Part A: Polymer Chemistry 41(24) (2003) 3941-3953.
[76] S.-C. Chen, Y.-C. Wu, F.-L. Mi, Y.-H. Lin, L.-C. Yu, H.-W. Sung, A novel pH-sensitive hydrogel composed of N, O-carboxymethyl chitosan and alginate cross-linked by genipin for protein drug delivery, Journal of Controlled Release 96(2) (2004) 285-300.
[77] F.-L. Mi, H.-W. Sung, S.-S. Shyu, Drug release from chitosan–alginate complex beads reinforced by a naturally occurring cross-linking agent, Carbohydrate Polymers 48(1) (2002) 61-72.
[78] Z. Zou, B. Zhang, X. Nie, Y. Cheng, Z. Hu, M. Liao, S. Li, A sodium alginate-based sustained-release IPN hydrogel and its applications, RSC advances 10(65) (2020) 39722-39730.
[79] S.V. Wanasinghe, E.M. Schreiber, A.M. Thompson, J.L. Sparks, D. Konkolewicz, Dynamic covalent chemistry for architecture changing interpenetrated and single networks, Polymer Chemistry 12(13) (2021) 1975-1982.
[80] A. Behravesh, M. Shahrousvand, A. Goudarzi, Poly (acrylic acid)/gum arabic/ZnO semi-IPN hydrogels: synthesis, characterization and their optimizations by response surface methodology, Iranian Polymer Journal 30(7) (2021) 655-674.
[81] G. Somya, P. Nayyar, B. Akanksha, S.P. Kumar, Interpenetrating polymer network-based drug delivery systems: emerging applications and recent patents, Egyptian Pharmaceutical Journal 14(2) (2015) 75.
[82] I. Ali, L. Ali Shah, S. Faizan, Investigation of the viscoelastic behavior of PVA-P (AAm/AMPS) IPN hydrogel with enhanced mechanical strength and excellent recoverability, Journal of Polymer Research 29(1) (2022) 1-12.
[83] A.S. Hoffman, Hydrogels for biomedical applications, Advanced drug delivery reviews 64 (2012) 18-23.
[84] G.A. Kumar, S.A. Wadood, S.D. Maurya, D. Ramchand, Interpenetrating polymeric network hydrogel for stomach-specific drug delivery of clarithromycin: Preparation and evaluation, Asian Journal of Pharmaceutics-October-December (2010).
[85] S.S. Vaghani, M.M. Patel, pH-sensitive hydrogels based on semi-interpenetrating network (semi-IPN) of chitosan and polyvinyl pyrrolidone for clarithromycin release, Drug development and industrial pharmacy 37(10) (2011) 1160-1169.
[86] R.V. Kulkarni, V. Sreedhar, S. Mutalik, C.M. Setty, B. Sa, Interpenetrating network hydrogel membranes of sodium alginate and poly (vinyl alcohol) for controlled release of prazosin hydrochloride through skin, International Journal of Biological Macromolecules 47(4) (2010) 520-527.
[87] A.P. Rokhade, N.B. Shelke, S.A. Patil, T.M. Aminabhavi, Novel interpenetrating polymer network microspheres of chitosan and methylcellulose for controlled release of theophylline, Carbohydrate Polymers 69(4) (2007) 678-687.
[88] Y. Zhang, J. Liu, L. Huang, Z. Wang, L. Wang, Design and performance of a sericin-alginate interpenetrating network hydrogel for cell and drug delivery, Scientific reports 5(1) (2015) 1-13.
[89] E.M. Ahmed, Hydrogel: Preparation, characterization, and applications: A review, Journal of advanced research 6(2) (2015) 105-121.
[90] F. Ullah, M.B.H. Othman, F. Javed, Z. Ahmad, H.M. Akil, Classification, processing and application of hydrogels: A review, Materials Science and Engineering: C 57 (2015) 414-433.
[91] U. Usta, R. Asmatulu, Hydrogels in various biomedical applications, Polymer Science: Research Advances, Practical Applications and Educational Aspects (2015) 248-257.
[92] A. Moghanian, A. Ghorbanoghli, M. Kazem-Rostami, A. Pazhouheshgar, E. Salari, M. Saghafi Yazdi, T. Alimardani, H. Jahani, F. Sharifian Jazi, M. Tahriri, Novel antibacterial Cu/Mg-substituted 58S-bioglass: Synthesis, characterization and investigation of in vitro bioactivity, International Journal of Applied Glass Science 11(4) (2020) 685-698.
[93] X. Liu, X. He, B. Yang, L. Lai, N. Chen, J. Hu, Q. Lu, Dual physically crosslinked hydrogels incorporating hydrophobic interactions with promising repairability and ultrahigh elongation, Advanced Functional Materials 31(3) (2021) 2008187.
[94] T. Watanabe, A. Ohtsuka, N. Murase, P. Barth, K. Gersonde, NMR studies on water and polymer diffusion in dextran gels. Influence of potassium ions on microstructure formation and gelation mechanism, Magnetic resonance in medicine 35(5) (1996) 697-705.
[95] A.V. Reis, M.R. Guilherme, O.A. Cavalcanti, A.F. Rubira, E.C. Muniz, Synthesis and characterization of pH-responsive hydrogels based on chemically modified Arabic gum polysaccharide, Polymer 47(6) (2006) 2023-2029.
[96] K. Varaprasad, G.M. Raghavendra, T. Jayaramudu, M.M. Yallapu, R. Sadiku, A mini review on hydrogels classification and recent developments in miscellaneous applications, Materials Science and Engineering: C 79 (2017) 958-971.
[97] A. Esmaeilkhanian, F. Sharifianjazi, A. Abouchenari, A. Rouhani, N. Parvin, M. Irani, Synthesis and characterization of natural nano-hydroxyapatite derived from turkey femur-bone waste, Applied biochemistry and biotechnology 189(3) (2019) 919-932.
[98] F. Sharifianjazi, N. Parvin, M. Tahriri, Synthesis and characteristics of sol-gel bioactive SiO2-P2O5-CaO-Ag2O glasses, Journal of Non-Crystalline Solids 476 (2017) 108-113.
[99] F. Sharifianjazi, A.H. Pakseresht, M.S. Asl, A. Esmaeilkhanian, H.W. Jang, M. Shokouhimehr, Hydroxyapatite consolidated by zirconia: applications for dental implant, Journal of Composites and Compounds 2(2) (2020) 26-34.
[100] S. De Jong, B. Van Eerdenbrugh, C.v. van Nostrum, J. Kettenes-Van Den Bosch, W. Hennink, Physically crosslinked dextran hydrogels by stereocomplex formation of lactic acid oligomers: degradation and protein release behavior, Journal of controlled release 71(3) (2001) 261-275.
[101] K. Saini, Preparation method, Properties and Crosslinking of hydrogel: a review, PharmaTutor 5(1) (2017) 27-36.

[102] B.F. Dizaji, M.H. Azerbaijan, N. Sheisi, P. Goleij, T. Mirmajidi, F. Chogan, M. Irani, F. Sharafian, Synthesis of PLGA/chitosan/zeolites and PLGA/chitosan/metal organic frameworks nanofibers for targeted delivery of Paclitaxel toward prostate cancer cells death, International journal of biological macromolecules 164 (2020) 1461-1474.
[103] R. Stenekes, H. Talsma, W. Hennink, Formation of dextran hydrogels by crystallization, Biomaterials 22(13) (2001) 1891-1898.
[104] M.F. Akhtar, M. Hanif, N.M. Ranjha, Methods of synthesis of hydrogels… A review, Saudi Pharmaceutical Journal 24(5) (2016) 554-559.
[105] M. Mihajlovic, M. Staropoli, M.-S. Appavou, H.M. Wyss, W. Pyckhout-Hintzen, R.P. Sijbesma, Tough supramolecular hydrogel based on strong hydrophobic interactions in a multiblock segmented copolymer, Macromolecules 50(8) (2017) 3333-3346.
[106] M.A. Haque, T. Kurokawa, G. Kamita, J.P. Gong, Lamellar bilayers as reversible sacrificial bonds to toughen hydrogel: hysteresis, self-recovery, fatigue resistance, and crack blunting, Macromolecules 44(22) (2011) 8916-8924.
[107] Y. Luo, Q. Wang, Recent development of chitosan-based polyelectrolyte complexes with natural polysaccharides for drug delivery, International journal of biological macromolecules 64 (2014) 353-367.
[108] T. Gotoh, K. Matsushima, K.-I. Kikuchi, Preparation of alginate–chitosan hybrid gel beads and adsorption of divalent metal ions, Chemosphere 55(1) (2004) 135-140.
[109] Y. Huang, H. Yu, C. Xiao, pH-sensitive cationic guar gum/poly (acrylic acid) polyelectrolyte hydrogels: Swelling and in vitro drug release, Carbohydrate polymers 69(4) (2007) 774-783.
[110] M. Ebara, Y. Kotsuchibashi, K. Uto, T. Aoyagi, Y.-J. Kim, R. Narain, N. Idota, J.M. Hoffman, Smart nanoassemblies and nanoparticles, Smart Biomaterials, Springer2014, pp. 67-113.
[111] S.S. Vaghani, M.M. Patel, pH-sensitive hydrogels based on semi-interpenetrating network (semi-IPN) of chitosan and polyvinyl pyrrolidone for clarithromycin release, Drug development and industrial pharmacy 37(10) (2011) 1160-9.
[112] R.V. Kulkarni, V. Sreedhar, S. Mutalik, C.M. Setty, B. Sa, Interpenetrating network hydrogel membranes of sodium alginate and poly(vinyl alcohol) for controlled release of prazosin hydrochloride through skin, International journal of biological macromolecules 47(4) (2010) 520-7.
[113] T.W. Chung, S.Y. Lin, D.Z. Liu, Y.C. Tyan, J.S. Yang, Sustained release of 5-FU from Poloxamer gels interpenetrated by crosslinking chitosan network, Int J Pharm 382(1-2) (2009) 39-44.
[114] Y. Zhang, J. Liu, L. Huang, Z. Wang, L. Wang, Design and performance of a sericin-alginate interpenetrating network hydrogel for cell and drug delivery, Scientific Reports 5(1) (2015) 12374.
[115] C.W. Yung, L.Q. Wu, J.A. Tullman, G.F. Payne, W.E. Bentley, T.A. Barbari, Transglutaminase crosslinked gelatin as a tissue engineering scaffold, Journal of biomedical materials research. Part A 83(4) (2007) 1039-1046.
[116] C.W. Yung, W.E. Bentley, T.A. Barbari, Diffusion of interleukin-2 from cells overlaid with cytocompatible enzyme-crosslinked gelatin hydrogels, Journal of biomedical materials research. Part A 95(1) (2010) 25-32.
[117] K.S. Kim, S.J. Park, J.A. Yang, J.H. Jeon, S.H. Bhang, B.S. Kim, S.K. Hahn, Injectable hyaluronic acid-tyramine hydrogels for the treatment of rheumatoid arthritis, Acta Biomater 7(2) (2011) 666-74.
[118] Y. Yeo, W. Geng, T. Ito, D.S. Kohane, J.A. Burdick, M. Radisic, Photocrosslinkable hydrogel for myocyte cell culture and injection, Journal of biomedical materials research. Part B, Applied biomaterials 81(2) (2007) 312-22.
[119] H.S. Yoo, Photo-cross-linkable and thermo-responsive hydrogels containing chitosan and Pluronic for sustained release of human growth hormone (hGH), Journal of biomaterials science. Polymer edition 18(11) (2007) 1429-41.
[120] J.I. Lee, H.S. Kim, H.S. Yoo, DNA nanogels composed of chitosan and Pluronic with thermo-sensitive and photo-crosslinking properties, Int J Pharm 373(1-2) (2009) 93-9.
[121] C. Hiemstra, L.J. van der Aa, Z. Zhong, P.J. Dijkstra, J. Feijen, Novel in Situ Forming, Degradable Dextran Hydrogels by Michael Addition Chemistry: Synthesis, Rheology, and Degradation, Macromolecules 40(4) (2007) 1165-1173.
[122] T. Ito, Y. Yeo, C.B. Highley, E. Bellas, C.A. Benitez, D.S. Kohane, The prevention of peritoneal adhesions by in situ cross-linking hydrogels of hyaluronic acid and cellulose derivatives, Biomaterials 28(6) (2007) 975-83.
[123] K.Y. Lee, E. Alsberg, D.J. Mooney, Degradable and injectable poly(aldehyde guluronate) hydrogels for bone tissue engineering, Journal of biomedical materials research 56(2) (2001) 228-33.
[124] K.K. Nishi, A. Jayakrishnan, Self-gelling primaquine-gum arabic conjugate: an injectable controlled delivery system for primaquine, Biomacromolecules 8(1) (2007) 84-90.
[125] M. Butler, Y.F. Ng, P. Pudney, Mechanism and kinetics of crosslinking reaction between biopolymers containing primary amine groups and genipin, Journal of Polymer Science Part A: Polymer Chemistry 41 (2003) 3941-3953.
[126] R. Parhi, Cross-Linked Hydrogel for Pharmaceutical Applications: A Review, Adv Pharm Bull 7(4) (2017) 515-530.
[127] K. Ono, Y. Saito, H. Yura, K. Ishikawa, A. Kurita, T. Akaike, M. Ishihara, Photocrosslinkable chitosan as a biological adhesive, Journal of biomedical materials research 49(2) (2000) 289-95.
[128] E.B. Denkbaş, M. Seyyal, E. Pişkin, Implantable 5-fluorouracil loaded chitosan scaffolds prepared by wet spinning, Journal of Membrane Science 172(1) (2000) 33-38.
[129] J. Li, X. Li, X. Ni, X. Wang, H. Li, K.W. Leong, Self-assembled supramolecular hydrogels formed by biodegradable PEO–PHB–PEO triblock copolymers and α-cyclodextrin for controlled drug delivery, Biomaterials 27(22) (2006) 4132-4140.
[130] G.W. Bos, J.J. Jacobs, J.W. Koten, S. Van Tomme, T. Veldhuis, C.F. van Nostrum, W. Den Otter, W.E. Hennink, In situ crosslinked biodegradable hydrogels loaded with IL-2 are effective tools for local IL-2 therapy, European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences 21(4) (2004) 561-7.
[131] V. Pazos, R. Mongrain, J.C. Tardif, Polyvinyl alcohol cryogel: optimizing the parameters of cryogenic treatment using hyperelastic models, Journal of the mechanical behavior of biomedical materials 2(5) (2009) 542-9.
[132] Meenakshi, M. Ahuja, Metronidazole loaded carboxymethyl tamarind kernel polysaccharide-polyvinyl alcohol cryogels: preparation and characterization, Int J Biol Macromol 72 (2015) 931-8.
[133] J.H. Sung, M.R. Hwang, J.O. Kim, J.H. Lee, Y.I. Kim, J.H. Kim, S.W. Chang, S.G. Jin, J.A. Kim, W.S. Lyoo, S.S. Han, S.K. Ku, C.S. Yong, H.G. Choi, Gel characterisation and in vivo evaluation of minocycline-loaded wound dressing with enhanced wound healing using polyvinyl alcohol and chitosan, Int J Pharm 392(1-2) (2010) 232-40.
[134] O.M. Păduraru, D. Ciolacu, R.N. Darie, C. Vasile, Synthesis and characterization of polyvinyl alcohol/cellulose cryogels and their testing as carriers for a bioactive component, Materials Science and Engineering: C 32(8) (2012) 2508-2515.
[135] J. You, S. Xie, J. Cao, H. Ge, M. Xu, L. Zhang, J. Zhou, Quaternized Chitosan/Poly(acrylic acid) Polyelectrolyte Complex Hydrogels with Tough, Self-Recovery, and Tunable Mechanical Properties, Macromolecules 49(3) (2016) 1049-1059.
[136] P.C. Chen, Y.J. Park, L.C. Chang, D.S. Kohane, R.H. Bartlett, R. Langer, V.C. Yang, Injectable microparticle-gel system for prolonged and localized lidocaine release. I. In vitro characterization, Journal of biomedical materials research. Part A 70(3) (2004) 412-9.
[137] Q.L. Li, Z.Q. Chen, B.W. Darvell, L.K. Liu, H.B. Jiang, Q. Zen, Q. Peng, G.M. Ou, Chitosan-phosphorylated chitosan polyelectrolyte complex hydrogel as an osteoblast carrier, Journal of biomedical materials research. Part B, Applied biomaterials 82(2) (2007) 481-6.
[138] D. Kulig, A. Zimoch-Korzycka, A. Jarmoluk, K. Marycz, Study on Alginate–Chitosan Complex Formed with Different Polymers Ratio, Polymers 8(5) (2016) 167.
[139] J. Antunes, R. Gonçalves, B. Ma, Chitosan/Poly(γ-glutamic acid) Polyelectrolyte Complexes: From Self- Assembly to Application in Biomolecules Delivery and Regenerative Medicine, Research & Reviews: Journal of Material Sciences 04 (2016) .
[140] S.R. Derkach, N.G. Voron'ko, N.I. Sokolan, The rheology of hydrogels based on chitosan–gelatin (bio)polyelectrolyte complexes, Journal of Dispersion Science and Technology 38(10) (2017) 1427-1434.
[141] Saleem, R.V. Kulkarni, N.G. Patil, Formulation and Evaluation of Chitosan Based Polyelectrolyte Complex Hydrogels for Extended Release of Metoprolol Tartrate, 2011.
[142] H.F. Liang, M.H. Hong, R.M. Ho, C.K. Chung, Y.H. Lin, C.H. Chen, H.W. Sung, Novel method using a temperature-sensitive polymer (methylcellulose) to thermally gel aqueous alginate as a pH-sensitive hydrogel, Biomacromolecules 5(5) (2004) 1917-25.
[143] N. Bhattarai, H.R. Ramay, J. Gunn, F.A. Matsen, M. Zhang, PEG-grafted chitosan as an injectable thermosensitive hydrogel for sustained protein release, Journal of controlled release : official journal of the Controlled Release Society 103(3) (2005) 609-24.
[144] J.W. Bae, D.H. Go, K.D. Park, S.J. Lee, Thermosensitive chitosan as an injectable carrier for local drug delivery, Macromolecular Research 14(4) (2006) 461-465.
[145] M. El-Badry, G. Fetih, D. Fathalla, F. Shakeel, Transdermal delivery of meloxicam using niosomal hydrogels: in vitro and pharmacodynamic evaluation, Pharmaceutical development and technology 20(7) (2015) 820-826.

[146] S.J. Buwalda, K.W.M. Boere, P.J. Dijkstra, J. Feijen, T. Vermonden, W.E. Hennink, Hydrogels in a historical perspective: From simple networks to smart materials, Journal of Controlled Release 190 (2014) 254-273.
[147] S. Khan, N.M. Ranjha, Effect of degree of cross-linking on swelling and on drug release of low viscous chitosan/poly (vinyl alcohol) hydrogels, Polymer bulletin 71(8) (2014) 2133-2158
[148] V.H. Pérez-Luna, O. González-Reynoso, Encapsulation of biological agents in hydrogels for therapeutic applications, Gels 4(3) (2018) 61.
[149] A. Onaciu, R.A. Munteanu, A.I. Moldovan, C.S. Moldovan, I. Berindan-Neagoe, Hydrogels based drug delivery synthesis, characterization and administration, Pharmaceutics 11(9) (2019) 432.
[150] B. Mishra, M. Upadhyay, S. Reddy Adena, B. Vasant, M. Muthu, Hydrogels: an introduction to a controlled drug delivery device, synthesis and application in drug delivery and tissue engineering, Austin J Biomed Eng 4(1) (2017) 1037-1049.
[151] J. Blöhbaum, I. Paulus, A.-C. Pöppler, J. Tessmar, J. Groll, Influence of charged groups on the cross-linking efficiency and release of guest molecules from thiol–ene cross-linked poly (2-oxazoline) hydrogels, Journal of materials chemistry B 7(10) (2019) 1782-1794.
[152] M. Mahinroosta, Z. Jomeh Farsangi, A. Allahverdi, Z. Shakoori, Hydrogels as intelligent materials: A brief review of synthesis, properties and applications, Materials Today Chemistry 8 (2018) 42-55.
[153] M. Rizwan, R. Yahya, A. Hassan, M. Yar, A.D. Azzahari, V. Selvanathan, F. Sonsudin, C.N. Abouloula, pH Sensitive Hydrogels in Drug Delivery: Brief History, Properties, Swelling, and Release Mechanism, Material Selection and Applications, Polymers 9(4) (2017) 137.
[154] Y. Huang, Z. Lin, M. Zheng, T. Wang, J. Yang, F. Yuan, X. Lu, L. Liu, D.J.J.o.P.S. Sun, Amorphous Fe_2O_3 nanoshells coated on carbonized bacterial cellulose nanofibers as a flexible anode for high-performance lithium ion batteries, 307 (2016) 649-656.
[155] M.B. Rahmany, M. Van Dyke, Biomimetic approaches to modulate cellular adhesion in biomaterials: A review, Acta biomaterialia 9(3) (2013) 5431-5437.
[156] M.M. Talukdar, I. Vinckier, P. Moldenaers, R. Kinget, Rheological characterization of xanthan gum and hydroxypropylmethyl cellulose with respect to controlled-release drug delivery, Journal of pharmaceutical sciences 85(5) (1996) 537-540.
[157] S. Khan, A. Ullah, K. Ullah, N.-u. Rehman, Insight into hydrogels, Designed monomers and polymers 19(5) (2016) 456-478.
[158] K.V.H. Prashanth, R.N. Tharanathan, Crosslinked chitosan—preparation and characterization, Carbohydrate research 341(1) (2006) 169-173.
[159] Y.P. Singh, N. Bhardwaj, B.B. Mandal, Potential of agarose/silk fibroin blended hydrogel for in vitro cartilage tissue engineering, ACS Applied Materials & Interfaces 8(33) (2016) 21236-21249.
[160] Z. Mohamadnia, M. Zohuriaan-Mehr, K. Kabiri, A. Jamshidi, H. Mobedi, pH-sensitive IPN hydrogel beads of carrageenan-alginate for controlled drug delivery, Journal of Bioactive and Compatible Polymers 22(3) (2007) 342-356.
[161] L. Yin, L. Fei, F. Cui, C. Tang, C. Yin, Superporous hydrogels containing poly (acrylic acid-co-acrylamide)/O-carboxymethyl chitosan interpenetrating polymer networks, Biomaterials 28(6) (2007) 1258-1266.
[162] S. Li, Y. Yang, X. Yang, H. Xu, In vitro degradation and protein release of semi-IPN hydrogels consisted of poly (acrylic acid-acrylamide-methacrylate) and amylose, Journal of applied polymer science 105(6) (2007) 3432-3438.
[163] P. Chivukula, K. Dušek, D. Wang, M. Dušková-Smrčková, P. Kopečková, J. Kopeček, Synthesis and characterization of novel aromatic azo bond-containing pH-sensitive and hydrolytically cleavable IPN hydrogels, Biomaterials 27(7) (2006) 1140-1151.
[164] C. Alvarez-Lorenzo, A. Concheiro, A.S. Dubovik, N.V. Grinberg, T.V. Burova, V.Y. Grinberg, Temperature-sensitive chitosan-poly (N-isopropylacrylamide) interpenetrated networks with enhanced loading capacity and controlled release properties, Journal of Controlled Release 102(3) (2005) 629-641.
[165] Y. Zhang, F. Wu, M. Li, E. Wang, pH switching on-off semi-IPN hydrogel based on cross-linked poly (acrylamide-co-acrylic acid) and linear polyallyamine, Polymer 46(18) (2005) 7695-7700.
[166] E. Ruel-Gariepy, J.-C. Leroux, In situ-forming hydrogels—review of temperature-sensitive systems, European Journal of Pharmaceutics and Biopharmaceutics 58(2) (2004) 409-426.
[167] S.R. Van Tomme, G. Storm, W.E. Hennink, In situ gelling hydrogels for pharmaceutical and biomedical applications, International journal of pharmaceutics 355(1-2) (2008) 1-18.
[168] N.E. Fedorovich, M.H. Oudshoorn, D. van Geemen, W.E. Hennink, J. Alblas, W.J. Dhert, The effect of photopolymerization on stem cells embedded in hydrogels, Biomaterials 30(3) (2009) 344-353.
[169] S.J. Bryant, C.R. Nuttelman, K.S. Anseth, Cytocompatibility of UV and visible light photoinitiating systems on cultured NIH/3T3 fibroblasts in vitro, Journal of Biomaterials Science, Polymer Edition 11(5) (2000) 439-457.
[170] Y. Murakami, M. Yokoyama, T. Okano, H. Nishida, Y. Tomizawa, M. Endo, H. Kurosawa, A novel synthetic tissue-adhesive hydrogel using a crosslinkable polymeric micelle, Journal of Biomedical Materials Research Part A 80(2) (2007) 421-427.
[171] V.S. Ghorpade, Preparation of hydrogels based on natural polymers via chemical reaction and cross-linking, Hydrogels Based on Natural Polymers, Elsevier2020, pp. 91-118.
[172] H. Kolb, M. G. Finn, KB Sharpless, Click Chemistry: Diverse Chemical Function from a Few Good Reactions, Angew. Chem. Int. Ed 40 (2001) 2004-2021.
[173] D.A. Ossipov, J. Hilborn, Poly (vinyl alcohol)-based hydrogels formed by "click chemistry", Macromolecules 39(5) (2006) 1709-1718.
[174] X.D. Xu, C.S. Chen, B. Lu, Z.C. Wang, S.X. Cheng, X.Z. Zhang, R.X. Zhuo, Modular synthesis of thermosensitive P (NIPAAm-co-HEMA)/β-CD based hydrogels via click chemistry, Macromolecular rapid communications 30(3) (2009) 157-164.
[175] W. Sheng, T. Liu, S. Liu, Q. Wang, X. Li, N. Guang, Temperature and pH responsive hydrogels based on polyethylene glycol analogues and poly (methacrylic acid) via click chemistry, Polymer International 64(10) (2015) 1415-1424.
[176] B.G. De Geest, W. Van Camp, F.E. Du Prez, S.C. De Smedt, J. Demeester, W.E. Hennink, Biodegradable microcapsules designed via 'click'chemistry, Chemical Communications (2) (2008) 190-192.
[177] C.D. Hermann, D.S. Wilson, K.A. Lawrence, X. Ning, R. Olivares-Navarrete, J.K. Williams, R.E. Guldberg, N. Murthy, Z. Schwartz, B.D. Boyan, Rapidly polymerizing injectable click hydrogel therapy to delay bone growth in a murine re-synostosis model, Biomaterials 35(36) (2014) 9698-9708.
[178] M.N. Ganivada, P. Kumar, R. Shunmugam, A unique polymeric gel by thiol–alkyne click chemistry, RSC Advances 5(62) (2015) 50001-50004.
[179] K.W. Boere, B.G. Soliman, D.T. Rijkers, W.E. Hennink, T. Vermonden, Thermoresponsive injectable hydrogels cross-linked by native chemical ligation, Macromolecules 47(7) (2014) 2430-2438.
[180] S. Mukherjee, M.R. Hill, B.S. Sumerlin, Self-healing hydrogels containing reversible oxime crosslinks, Soft matter 11(30) (2015) 6152-6161.
[181] M. Fan, Y. Ma, Z. Zhang, J. Mao, H. Tan, X. Hu, Biodegradable hyaluronic acid hydrogels to control release of dexamethasone through aqueous Diels–Alder chemistry for adipose tissue engineering, Materials Science and Engineering: C 56 (2015) 311-317.
[182] D.E. Ciolacu, R. Nicu, F. Ciolacu, Cellulose-based hydrogels as sustained drug-delivery systems, Materials 13(22) (2020) 5270.
[183] M.C. Koetting, J.T. Peters, S.D. Steichen, N.A. Peppas, Stimulus-responsive hydrogels: Theory, modern advances, and applications, Materials Science and Engineering: R: Reports 93 (2015) 1-49.
[184] Q. Chai, Y. Jiao, X. Yu, Hydrogels for biomedical applications: their characteristics and the mechanisms behind them, Gels 3(1) (2017) 6.
[185] S. Choudhary, J.M. Reck, A.J. Carr, S.R. Bhatia, Hydrophobically modified alginate for extended release of pharmaceuticals, Polymers for Advanced Technologies 29(1) (2018) 198-204.
[186] M.P. Di Cagno, F. Clarelli, J. Våbenø, C. Lesley, S.D. Rahman, J. Cauzzo, E. Franceschinis, N. Realdon, P.C. Stein, Experimental determination of drug diffusion coefficients in unstirred aqueous environments by temporally resolved concentration measurements, Molecular pharmaceutics 15(4) (2018) 1488-1494.
[187] S. Kirchhof, M. Abrami, V. Messmann, N. Hammer, A.M. Goepferich, M. Grassi, F.P. Brandl, Diels–Alder hydrogels for controlled antibody release: correlation between mesh size and release rate, Molecular Pharmaceutics 12(9) (2015) 3358-3368.
[188] Y. Wu, S. Joseph, N. Aluru, Effect of cross-linking on the diffusion of water, ions, and small molecules in hydrogels, The Journal of Physical Chemistry B 113(11) (2009) 3512-3520.
[189] M. Bansal, A. Dravid, Z. Aqrawe, J. Montgomery, Z. Wu, D. Svirskis, Conducting polymer hydrogels for electrically responsive drug delivery, Journal of Controlled Release 328 (2020) 192-209.
[190] M. Young, P. Carroad, R. Bell, Estimation of diffusion coefficients of proteins, Biotechnology and bioengineering 22(5) (1980) 947-955.
[191] B.E. Jensen, K. Edlund, A.N. Zelikin, Micro-structured, spontaneously eroding hydrogels accelerate endothelialization through presentation of conjugated growth factors, Biomaterials 49 (2015) 113-124.
[192] R. Chandrawati, Enzyme-responsive polymer hydrogels for therapeutic delivery, Experimental Biology and Medicine 241(9) (2016) 972-979.
[193] S.P. Zustiak, J.B. Leach, Characterization of protein release from hydrolytically degradable poly (ethylene glycol) hydrogels, Biotechnology and bioengi-

neering 108(1) (2011) 197-206.
[194] S. Sheth, E. Barnard, B. Hyatt, M. Rathinam, S.P. Zustiak, Predicting Drug Release from Degradable Hydrogels Using Fluorescence Correlation Spectroscopy and Mathematical Modeling, Frontiers in bioengineering and biotechnology (2019) 410.
[195] M. Hamidi, A. Azadi, P. Rafiei, Hydrogel nanoparticles in drug delivery, Advanced drug delivery reviews 60(15) (2008) 1638-1649.
[196] L. Zhang, G. Zhang, J. Lu, H. Liang, Preparation and characterization of carboxymethyl cellulose/polyvinyl alcohol blend film as a potential coating material, Polymer-Plastics Technology and Engineering 52(2) (2013) 163-167.
[197] X. Qiu, S. Tao, X. Ren, S. Hu, Modified cellulose films with controlled permeatability and biodegradability by crosslinking with toluene diisocyanate under homogeneous conditions, Carbohydrate polymers 88(4) (2012) 1272-1280.
[198] H. Huang, X. Qi, Y. Chen, Z. Wu, Thermo-sensitive hydrogels for delivering biotherapeutic molecules: A review, Saudi Pharmaceutical Journal 27(7) (2019) 990-999.
[199] N. Kamaly, B. Yameen, J. Wu, O.C. Farokhzad, Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release, Chemical reviews 116(4) (2016) 2602-2663.
[200] S. Sim, A. Figueiras, F. Veiga, Modular hydrogels for drug delivery, (2012).
[201] N. Das, Biodegradable hydrogels for controlled drug delivery, Mondal IM, editions. Cellulose-based superabsorbent hydrogels. Springer Nature (2018) 1-41.
[202] Q. Jiang, N. Reddy, Y. Yang, Cytocompatible cross-linking of electrospun zein fibers for the development of water-stable tissue engineering scaffolds, Acta biomaterialia 6(10) (2010) 4042-4051.
[203] T.M. O'Shea, A.A. Aimetti, E. Kim, V. Yesilyurt, R. Langer, Synthesis and characterization of a library of in-situ curing, nonswelling ethoxylated polyol thiol-ene hydrogels for tailorable macromolecule delivery, Advanced Materials 27(1) (2015) 65-72.
[204] H.K. Lau, A. Paul, I. Sidhu, L. Li, C.R. Sabanayagam, S.H. Parekh, K.L. Kiick, Microstructured Elastomer-PEG Hydrogels via Kinetic Capture of Aqueous Liquid–Liquid Phase Separation, Advanced Science 5(6) (2018) 1701010.
[205] M.K. Nguyen, O. Jeon, M.D. Krebs, D. Schapira, E. Alsberg, Sustained localized presentation of RNA interfering molecules from in situ forming hydrogels to guide stem cell osteogenic differentiation, Biomaterials 35(24) (2014) 6278-6286.
[206] T. Saito, Y. Tabata, Preparation of gelatin hydrogels incorporating small interfering RNA for the controlled release, Journal of drug targeting 20(10) (2012) 864-872.
[207] F.M. Carbinatto, A.D. de Castro, R.C. Evangelista, B.S. Cury, Insights into the swelling process and drug release mechanisms from cross-linked pectin/high amylose starch matrices, Asian Journal of Pharmaceutical Sciences 9(1) (2014) 27-34.
[208] I. Gibas, H. Janik, Synthetic polymer hydrogels for biomedical applications, (2010).
[209] S.V. Sawant, S.V. Sankpal, K.R. Jadhav, V.J. Kadam, Hydrogel as drug delivery system, Research Journal of Pharmacy and Technology 5(5) (2012) 561-569.
[210] H. Hezaveh, I.I. Muhamad, I. Noshadi, L. Shu Fen, N. Ngadi, Swelling behaviour and controlled drug release from cross-linked κ-carrageenan/NaCMC hydrogel by diffusion mechanism, Journal of microencapsulation 29(4) (2012) 368-379.