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Crosslinked natural hydrogels for drug delivery systems

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ABSTRACT

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

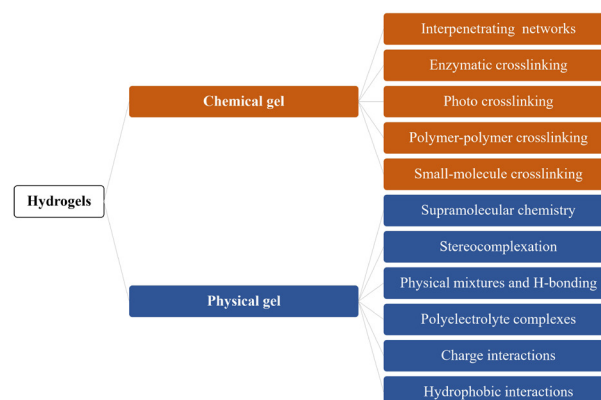


Fig. 1. Hydrogels classification according to crosslinking methods.

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.

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 NH₂), 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/NH₂ 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 α -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 H₂O₂ presence. In this process, HRP binds rapidly with H₂O₂ 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 H₂O₂ 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 H₂O₂ 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 (-N₃) 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 (CH₂=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 argininyglycylaspartic 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 complexation, 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 DDS 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		Modified PEG-chitosan	[118]	
Human growth hormone (hGH)		Photo crosslinking	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]	
Propranolol 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]	
----		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]	
----		Polyelectrolyte complexes	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]	

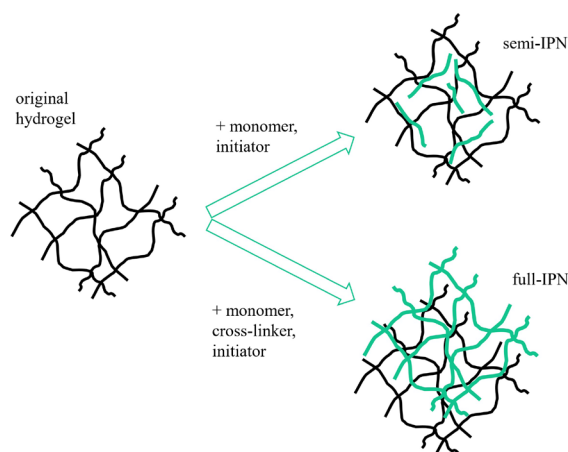


Fig. 2. Full- and semi-IPN structure and formation.

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 pre-made 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].

Biorthogonal, 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 cycloaddition, 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 ($r_{\text{mesh}}/r_{\text{drug}} > 1$), 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):

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

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 ($r_{\text{mesh}}/r_{\text{drug}} \approx 1$) 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 ($r_{\text{mesh}}/r_{\text{drug}} < 1$) [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.

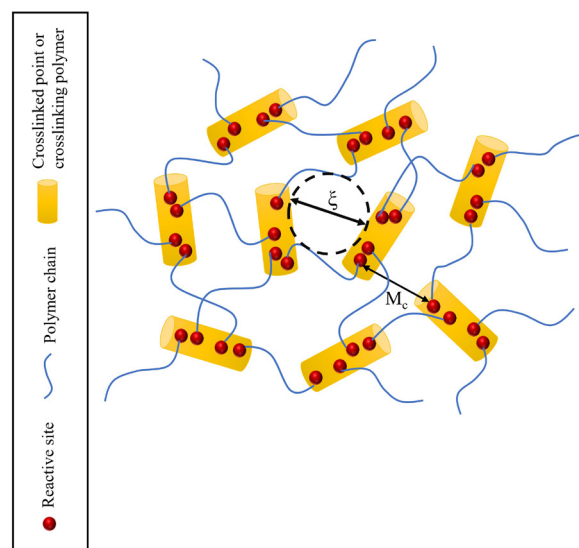


Fig. 3. Illustration of a hydrogel consisting of hydrophilic polymer chains joined by crosslink sites or crosslinking polymers.

[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 $-\text{SO}_3\text{H}$, $-\text{COOH}$, $-\text{NH}_2$, and $-\text{OH}$). 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 cross-linked 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 ($v_{2,s}$).
- The number of average molecular weight crosslinks per molecule (M_c)
- The size of the network mesh (ξ) (Fig. 3).

κ Carrageenan 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 κ C/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.

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