Technical Features of Polysaccharide-Based Hydrogels in Drug Delivery

Subjects: Chemistry, Medicinal | Chemistry, Organic | Nanoscience & Nanotechnology

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Hydrogels are a form of highly hydrophilic biomaterials with three-dimensional architecture that can retain a significant amount of water and swell without disintegrating. Hydrogels can be either synthetic, natural, or hybrid forms. Natural polymer hydrogels are those derived from naturally sourced polymers, including polysaccharides, polynucleotides, and proteins. Neutral, cationic, and anionic categories describe the chemical properties of natural sources of polymers. These polymers are easily accessible, ubiquitous, affordable, non-toxic, renewable, and have other appealing biological features.

Keywords: polysaccharide ; drug delivery ; hydrogel ; bioengineering

1. Biochemical Characteristics of Polysaccharide-Based Hydrogels

Based on their chemical structure, hydrogels are classified into several classes: Polysaccharides (e.g., cellulose, starch, gums), biological polymers (DNA), polyamides (collagen), polyphenols (lignin), organic/inorganic polyesters, and polyanhydrides [1]. Essential aspects of the hydrogels include strength, stiffness, relative biocompatibility, biodegradability, ability to absorb water (swell), and stimuli responsiveness. These qualities are critical for electro–biochemical applications. As Varghese et al. revealed, both synthetic hydrogel and biological soft tissue are “soft and wet” materials since they are both spongy and wet. However, biological tissue, such as muscle, displays several types of functionalities, and hydrogels typically perform poorly [2]. This is partly because biological tissue has a complicated structure, whereas most hydrogels are amorphous.

Furthermore, the cytotoxicity of biocompatible material is crucial for its usage in biomedical utilization. Polysaccharide-based hydrogels, however, ought to be biodegradable and nontoxic. Biocompatibility is the capacity of a material to engage effectively with the host tissues and react accordingly in a particular setting. Bashir et al. represent that biosafety and bio-functionality are the major fundamental elements of biocompatibility. If the hydrogels do not comply with these requirements, they can become damaged. Toxic chemicals used to prepare hydrogel formulations frequently generate in vivo biocompatibility issues [3]. In addition, polysaccharides have been considered safe for food applications since they are non-toxic. In addition, biodegradable hydrogels are an absolute necessity in the biomedical industry. Likewise, polysaccharide-based hydrogels are considered biodegradable if organisms can break them down into inactive byproducts. The moieties are determined by the systems and the technique of synthesis. Degradation processes include hydrolysis and solubilization of biological entities of hydrogels to yield end products. Based on Ahmad et al.’s results, bio-absorption and bio-erosion may lead the hydrogels being disintegrated and easily removed from the body [4].

2. Chemically and Physical Crosslinked Polysaccharide-Based Hydrogels

Chemical cross-linkable hydrogels are a form of hydrogel that may be covalently bonded from a liquid to a solid. To produce hydrogels chemically, this approach employs many reactions, including optical polymerization, enzyme reactions, and click reactions. Because of their high mechanical strength, chemical cross-linked hydrogels have been investigated and employed in various areas such as pharmaceuticals, agriculture, food processing, and cosmetology [5]. Physical hydrogels are formed by interacting with molecular entanglements and/or additional forces such as ionic, H-bonding, or hydrophobic interactions. Since these connections are weak, physical hydrogels are classified as reversible gels. These are made without applying cross-linking reagent chemical changes. Physically cross-linked hydrogels are more susceptible to degradation. Based on the work of Parhi et al., unlike chemical crosslinked hydrogels, physical ones are homogeneous. These gels are very promising for introducing bioactive compounds [6].

3. Swelling Properties of Polysaccharide-Based Hydrogels

Polysaccharide-based hydrogels can potentially absorb liquids owing to the cross-linked polymeric materials in their structures. This capacity, based on ionic groups in the body—the larger number of ionic groups can lead to a higher capacity of holding water—plays a critical role in transferring nutrients and cellular products throughout the hydrogel and makes releasing drugs from hydrogels more efficient [7]. In addition, Suflet et al. (2021) showed that covalent association with physical cross-linking techniques could form hydrogels with the advantages of fast-swelling and low-elastic modulus [8]. Moreover, the equilibrium and swelling kinetics can be affected by various variables, including cross-linking ratio, ionic interactions, synthesis process, and polymeric chemical bonding. To assess the swelling qualities of hydrogels, the swelling ratio, which is the weight-swelling ratio of swollen gel to dry gel, is used. It is essential to consider that cross-linking determines the swelling ratio of a hydrogel. Hamdy et al. revealed that strongly cross-linked polymers exhibit a lower swelling ratio and poorly cross-linked polymers have a higher swelling ratio. Additionally, the presence of hydrophobic and hydrophilic groups and the chemical structure of hydrogels determines their swelling behavior. Polysaccharide-based hydrogels with more hydrophilic groups swell more than hydrogels with more hydrophobic groups [9].

4. The Elasticity of Polysaccharide-Based Hydrogels

Elasticity is another main characteristic of hydrogels derived from not only cross-linking and charge densities of the polymeric network matrix but also the accumulation of a cross-linked polymer matrix that can happen to hydrogels when the synthetic procedure is performed. Hence, hydrogels can save their basic forms after stopping forces from making strain [10]. In this regard, Qian et al. designed a simple and environmentally friendly process for making hydrogels from polysaccharides that can serve as novel drug carriers. A reversible chemical link was formed between carboxyethyl-modified chitosan (CEC) and aldehyde-modified hyaluronic acid (A-HA) loaded with doxorubicin to create the hydrogels. This elastic and self-healing hydrogel is an intriguing contender as a drug delivery carrier [11].

5. Mechanical Properties of Polysaccharide-Based Hydrogels

This characteristic of hydrogels arises from the degree of cross-linking in their structure that causes stiff hydrogels if there are many incidences of cross-linking in the structure, while few instances of cross-linking can cause soft hydrogels. Therefore, they may play a key role in the mechanical properties of hydrogels making them capable of performing functional activities, including repairing ligaments and tendons, wound healing, tissue engineering, drug delivery systems (DDSs), and being an appropriate option for replacing cartilage structures [12]. Here, Singh et al. reported the synthesis of an *Acacia* gum polysaccharide-based hydrogel for wound dressings with high mechanical strength [13].

6. Biocompatibility and Bioactivity of Polysaccharide-Based Hydrogels

Biocompatibility and bioactivity arising from the attendance of freely accessible groups such as carboxyl (–COOH), amino ($–NH_3$), and hydroxyl (–OH) leading to some functional chemical adjustments are the reasons that make it possible for hydrogels to be used in the biomedical area of studies. This means the suitable hydrogels should not only pass the biosafety test but also provide systematic feedback that is fitted on the host cells and enclosed tissues [14]. For example, to develop controlled drug delivery systems, Ali et al. created a hydrogel made of citric acid cross-linked polysaccharide from *Salvia Spinosa* L. that is pH-sensitive, biocompatible, and non-toxic [15].

7. Inhomogeneity of Polysaccharide-Based Hydrogels

Homogeneity of hydrogels can be defined as a sort of hydrogel with uniform distribution of cross-linking in their matrix, and inhomogeneity of hydrogels that do not follow this rule are noticed as spatial inhomogeneity that can have negative impacts on the efficacy of hydrogels' functions. To be more specific, uneven arrangement of cross-linking can cause diminishment of the visual appearance and strength of the hydrogel [16]. Kopač et al. found that hydrogels always exhibit an inhomogeneous cross-link density distribution, another imperfection that isn't accounted for in the Peppas-Merrill equation. Rheological measures can be used to characterize the cross-link concentration of hydrogels, while LF-NMR analysis can efficiently assess the gel inhomogeneity in drug delivery systems [17].

8. Absorption under Load (AUL)

The highest AUL is a factor showing how much moisture can be absorbed by a polymer under pressure. Based on work by Kim et al., the thickness of surface cross-linking can positively affect the factor of AUL. In addition, if the time of surface

cross-linking increases, AUL will also be improved, which is an important factor in DDSs [18].

9. Molding Time

Hydrogels can be created quickly from physical cross-linking that rapid ionic gelation, for example, can make clearer. However, chemical cross-linking may lead to more stable and persistent hydrogels. Zakerikhoob et al. made hydrogels according to in situ alginates, which had the potential to soak up liquid and gel them much more quickly than other sorts of hydrogels. It is important to say that such characteristics of hydrogels allow them to be regarded as perfect-matched options for use in pharmaceutical science as well as health-related fields [19].

10. Self-Assembled Supramolecular Polysaccharide-Based Hydrogels

Inspired by nature, self-assembled hydrogels regulated by weak, intermolecular interactions have garnered much attention for generating systems with ordered structures and functionalities. These efforts have resulted in various self-assembled functional materials, including liquids, elastomers, gels, and hard materials. Most biopolymers, including collagen and nucleic acids, use molecular conformations to generate higher-order patterns and respond to small changes in environmental stimuli. Human-made macromolecules having similar effects have been the subject of extensive research because of the novel properties they bring to the field. One of the earliest examples of these structures includes polymer hydrogels, cross-linked networks of macromolecules that undergo reversible transitions in reaction to minor environmental changes. Thus, supramolecular hydrogels are a self-assembled network structure created by non-covalent bonds. Because of their ability to undergo sol–gel and/or gel–sol transitions in response to minor changes in their surroundings, these hydrogels are considered smart. Hoque et al. revealed that stimuli-responsive hydrogels represent fascinating substances with potential uses in biomedical engineering, DDSs to improve innate tissue regeneration, and medical diagnostics imaging [20].

11. pH Sensitivity of Polysaccharide-Based Hydrogels

A pH-sensitive hydrogel is a gel construction that responds to pH alteration. Hydrogels may often either expand or shrink in response to a shift in the chemically reactive environment. Hydrogels can be created utilizing in situ polymerization processes, making them ideal for implementation into microfluidic devices. These pH-sensitive hydrogels have applications in creating pH-sensitive control valves, systems that can release a substance when the pH is changed. pH-responsive hydrogels are a biomaterial with advantageous chemical and physical features at certain pH levels. Polymer chains are linked with acidic or basic groups. Hydrogels can release drugs in three distinct ways: through diffusion, swelling, and chemically triggered methods. Most people are comfortable with the diffusion-regulated approach, which bases its drug release model on Fick's law of diffusing. When the drug molecules' molecular dimensions are much smaller than the pore size of the permeable hydrogels, the hydrogels' permeability is proportional to their diffusion coefficient. When the porous structure in the hydrogels and the size of the drugs are close, the cross-linked polymer chains inhibit drug molecule release [21].

Consequently, when the swelling rate is greater than the release rate of the drug, the swelling controls drug release [22]; this includes water molecule absorption followed by drug desorption. The sensitivity of dry (glassy) polymer hydrogels to modifying shape and volume during hydration regulates the drug release rate, which controls the hydrogel content and cross-linking density. Hydrogels are structures that allow water or other physiological fluids to permeate their interfaces thanks to free intermolecular linkages. The swelling results from the tension created by the circulating solvent, which causes the space between the polymer chains to increase (polymer chain relaxation). After the drug has been slowly released, the swelling will go away due to desorption [23].

One exampleis transdermal drug delivery. The outermost layer of skin, termed as stratum corneum, has many features such as cohesion, intercellular lipids, permeability and so on. It is affected by many factors such as pH of the skin. The normal pH of skin is in the index of 5.0–6.0, and this is why the stratum corneum is considered an acid mantle. The acid mantle changes due to many factors such as age, gender, sebaceous glands, apocrine glands, eccrine glands, and epidermal cells. These factors lead to various disorders such as acne or inflammation. High skin pH causes micellization (>6.0) while a pH under 4.5 results in structural disorders. Patch dermal therapy is extremely crucial, especically to prevent side effects when longer administration is necessary. Hence, Kwon et al. prepared pH-sensitive hydroxyethyl cellulose/hyaluronic acid (HECHA) composite hydrogels cross-linked with divinyl sulfone to control drug release of isoliquiritigenin (ILTG) to treat propionibacterium acnes [23].

12. Polysaccharide-Based Hydrogels with Temperature-Sensitivity Feature

It has been discovered that the tumor, ischemia, and wound healing sites are acidic. Therefore, researchers have been motivated to create medication delivery methods that may specifically target areas of local acidosis through dual pH and temperature-sensitive hydrogels. The temperature-sensitivity in thermally sensitive hydrogels is mediated by the delicate balance of hydrophobic and hydrophilic components of the polymer monomer, which has both hydrophobic and hydrophilic aspects in its framework [24]. The dissolution of the cross-linked system and the sol–gel phase separation are modified as a function of temperature due to changes in the interactions of the hydrophilic and hydrophobic segments of the polymer with water molecules. The gel phase is stable and does not migrate compared to the moving sol phase. The macroscopic dissolved phase of a cross-linking network in an aqueous solution is identified by shifting the balance of hydrophilicity and hydrophobicity. Mechanisms on a micro level related to thermo-sensitive subunits can be employed to obtain the gelation capability of thermo-sensitive hydrogels at either the lower critical solution temperature or the upper critical solution temperature (UCST); hydrogels separate from the solution and solid. The polymer is soluble in the presence of a lower critical solution temperature (LCST), but it begins to shrink, becoming hydrophobic and insoluble, in the presence of an LCST, leading to gel formation. Instead, the UCST can be found in the hydrogel formed when the polymer solution is cooled. Specifically, the polymer in solution undergoes a phase shift, changing from a soluble (random coil) to an insoluble state (collapse or micelle form) as it approaches the critical temperature. The ratio of hydrophilic to hydrophobic groups determines the LCST. Hydrogels that release their bioactive ingredients constantly based on temperature have seen significant development [25]. Thermo-sensitive gels offer many benefits as a delivery mechanism. Despite typical hydrogels that must be surgically placed, the temperature-sensitive properties of the hydrogel enable delivery, preventing first-pass metabolism. The heat-responsive gel is preferable for injectable applications because it does not require any denaturing cross-linking agent; additionally, the temperature-induced sol–gel transition is entirely safe when occurring inside the body. Encapsulation in a flowing form provides homogeneous dispersion of therapeutic drugs in hydrogels. In contrast, quick sol-to-gel transition at body temperature avoids early burst release of therapeutics, allowing for controlled-release behavior. Moreover, the flowable administration gives the hydrogel form stability [24].

13. Affinity of Polysaccharide-Based Hydrogels

The functionalization of hydrogels with ligands results in affinity hydrogels (heparin, peptides, and aptamers are a few examples). Because of the strong protein–ligand binding, affinity hydrogels can retain protein permanently. They primarily control protein or drug molecules released through a diffusion-coupled binding reaction. Using particular activating molecules, affinity hydrogels can be designed to gain biomimetic intellect for on-demand protein release [26]. Rial-Hermida et al. reported that the mechanism of affinity-based delivery exploits the interactions between the biotherapeutic drug and the delivery device. These interactions can be advantageous bilaterally, in both incorporation and release of active drugs. In these instances, the release can be controlled by the intensity of the affinity contacts, the concentration of the binding ligand, the characteristic of dissociation of the synthesized complexes, and the size and shape of the hydrogel [27].

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