Potential Biopolymers for Designing Hydrogel in Tissue Engineering and Cancer Therapy: An Overview

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Abstract

Hydrogels derived from biopolymers are not only easily synthesized but can also be tailored with specific characteristics for a broad spectrum of applications, particularly in the biomedical field where they have proven instrumental in enhancing patient care and outcomes. Biopolymers such as polysaccharides, polypeptides, and nucleic acids can be engineered into hydrogels, each serving distinct purposes based on their inherent properties. For instance, collagen, gelatin, and elastin are prominent examples of polypeptide-based hydrogels, while alginate, cellulose, and glycosaminoglycan represent key polysaccharide-based variants. The development and application of hydrogels have been underpinned by various theoretical frameworks, including the Flory-Rehner theory and Rubber Elasticity Theory, which, along with calculations of porosity and pore size, offer a deep understanding of their structural characteristics. The fabrication of hydrogels is typically a straightforward process involving the homogeneous mixing of selected chemicals, tailored to the desired function of the final product. The diversity of hydrogel types, each with its distinct biomedical applications, highlights the versatility and potential of these materials. This overview not only encapsulates the recent advancements in biopolymer-based hydrogels but also suggests future avenues for their application in advanced medical therapies, paving the way for innovative treatments and improved patient outcomes.

Keywords: *Biopolymer; Hydrogel; Tissue Engineering; Cancer treatment*

1. Introduction

Biopolymers are naturally occurring macromolecules composed of numerous repeating monomeric units, which are synthesized within living organisms. These polymers play essential roles in various biological processes and are fundamental components of all living cells. These polymers are typically derived from plant and animal sources, which contributes to their biodegradability and renewability, making them highly advantageous for various applications [1, 2].

Biopolymers play a multitude of vital roles within the human body, contributing to various essential physiological processes. One of their primary functions is the formation of tissues composed of cells. In addition to forming tissues, biopolymers are crucial for the proper functioning of connective tissues, such as human cartilage. Hyaluronic acid, a biopolymer found in cartilage, serves as a lubricant and shock absorber within joints, ensuring smooth movement and protecting joint surfaces from wear and tear. Furthermore, biopolymers are integral to the endocrine system, where they act as signaling molecules [3]. The individual monomers of biopolymers are covalently bonded, allowing the polymer structures to grow longer and perform various functions. For example, nucleic acids such as DNA and RNA are composed of nucleotide monomers and are essential for storing and transmitting genetic information. Proteins, or polypeptides, are made from amino acids linked by peptide bonds and are encoded by nucleic acids; they are involved in a wide range of biological functions, including enzymatic activity and structural support. Additionally, polysaccharides, which are complex carbohydrates made up of monosaccharide units, include cellulose in plant cell walls, starch for energy storage in plants, and glycogen in animals. These biopolymers are crucial for numerous biological processes and the overall molecular architecture of life [4].

Hydrogels are extensively employed in a broad range of disciplines, owing to their distinctive structural characteristics and their ability to adapt to a wide array of environmental conditions [5, 6]. Their inherent flexibility is the defining feature that elevates hydrogels above other biomaterials, providing an unmatched versatility that extends their utility from industrial sectors to biomedical applications. This adaptability is particularly evident in the development of drug delivery systems, where hydrogels enable precise, controlled release of therapeutic agents, thereby enhancing efficacy and patient outcomes. Moreover, hydrogels play a crucial role in environmental applications, particularly in the removal of dyes and heavy metals from wastewater. Their ability to selectively adsorb and retain pollutants underscores their importance in sustainable environmental management. In the field of tissue engineering, hydrogels serve as scaffolds that mimic the extracellular matrix, supporting cell growth and tissue regeneration, which is vital for the advancement of regenerative medicine. Additionally, the application of hydrogels in the production of contact lenses further exemplifies their versatility. The unique combination of softness, permeability, and biocompatibility makes hydrogels the material of choice for creating lenses that provide comfort and enhance visual acuity. Across these diverse applications, the unique properties of hydrogels continue to drive innovation and progress in both industrial and biomedical fields [5-7].

Biopolymers are indispensable in the fabrication of sophisticated hydrogels, particularly those designed for superior biocompatibility [8]. The role of these naturally derived polymers is paramount, as they provide the foundational structure and functionality needed for creating hydrogels with enhanced performance. Sugar-based polysaccharides and protein-based polypeptides, in particular, have emerged as essential components in the synthesis of innovative, biodegradable, and biocompatible hydrogel systems.

Polysaccharides, such as cellulose, alginate, and glycosaminoglycans, are extensively utilised due to their inherent ability to form hydrogels with robust mechanical properties and excellent water retention capabilities. Cellulose, for instance, is prized for its strength and rigidity, making it a key ingredient in hydrogels designed for structural applications. Alginate, derived from brown algae, is favoured for its ability to gel in the presence of divalent cations, making it highly valuable in biomedical applications where in situ gelation is required. Glycosaminoglycans, with their complex sugar structures, are particularly effective in mimicking the natural extracellular matrix, thereby enhancing cell compatibility and promoting tissue regeneration. Similarly, protein-based polypeptides such as collagen, gelatin, and elastin play a critical role in hydrogel engineering. Collagen, the most abundant protein in the human body, provides hydrogels with exceptional tensile strength and biocompatibility, making it ideal for applications in wound healing and tissue scaffolding. Gelatin, a denatured form of collagen, offers similar benefits but with greater flexibility and ease of manipulation, which is advantageous in the development of injectable hydrogels. Elastin, known for its elastic properties, imparts hydrogels with the ability to withstand repeated mechanical stress, making it suitable for dynamic tissue environments. Each of these biopolymers brings its own distinct advantages and structural attributes, enabling the creation of a wide array of hydrogels that can be precisely tailored to specific requirements [9].

In this overview, we will provide a comprehensive definition of hydrogels, explore various hydrogels, and examine their diverse applications, with a particular focus on biomedical uses. The discussion will encompass a range of hydrogels, highlighting those synthesised from both polypeptide and polysaccharide biopolymers. Through this analysis, we aim to elucidate the unique properties and potential of these materials in advancing biomedical technologies.

2. Various Biopolymers

2.1 Polypeptides

Polypeptides, more commonly referred to as proteins, are complex molecules composed of long chains of amino acids linked by amide bonds. These chains can aggregate into functional proteins through either the assembly of multiple polypeptide chains or the folding of a single chain into a specific three-dimensional structure. Polypeptides play a crucial role in biological systems, being fundamental to the creation and function of enzymes, tissues, and muscle structures [10].

Collagen

Collagen stands out as one of the principal proteins within the extracellular matrix (ECM) [11]. Its primary function in the ECM is to provide structural support, which makes it an excellent candidate for use in scaffolding and hydrogel applications. Collagen is characterised by its trimeric molecular structure, which consists of three intertwined alpha-helices [12]. The strength and stability of collagen are largely attributed to the extensive hydrogen bonding within the triple helix, which endows it with substantial tensile strength.

However, it is noteworthy that while some degree of crosslinking is beneficial for collagen's structural stability, excessive crosslinking can lead to increased brittleness—a phenomenon often associated with ageing and the deterioration of tissue quality [13].

Gelatin

Gelatin is derived from collagen through a process that involves breaking down the collagen structure. The properties of gelatin, such as its molecular weight and isoelectric point, are influenced by the source of collagen and the method of extraction. Typically, gelatin extraction involves treating collagen with basic, acidic, or enzymatic solutions to cleave the cross-links that stabilise the collagen matrix. Acidic treatments produce gelatin with an isoelectric point around 8–9 ("type A"), whereas basic treatments yield gelatin with an isoelectric point of 4–5 ("type B") [14-16]. The extraction conditions, including temperature, pH, and processing duration, can be optimised to control the extent of collagen conversion into gelatin [17-19]. Gelatin-based hydrogels are notable for their self-healing properties, high biocompatibility, and biodegradability, making them suitable for various therapeutic applications, including injectable formulations [19].

2.2 Polysaccharides

Polysaccharides are complex carbohydrates composed of multiple monosaccharide units covalently bonded through glycosidic linkages. These macromolecules are integral to biological systems, contributing to structural support within cells and organs as well as serving as energy reserves [20].

Alginate

Alginate, a polysaccharide predominantly extracted from brown seaweed (*Phaeophyceae*), is highly valued in hydrogel technology due to its favourable biocompatibility and gelation properties [21]. The extraction process typically involves treating the seaweed with sodium hydroxide (NaOH) and subsequently precipitating the alginate with calcium chloride. The resulting alginate can be further enhanced through a process involving heavy metal ion absorption, which significantly strengthens the hydrogel compared to non-absorbed forms. This modification improves the overall performance of the alginate hydrogels, making them more effective for various recovery and biomedical applications [22].

2.3 Nucleic Acids

Nucleic acids, which include deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), are essential macromolecules present in all living cells and many viruses [23, 24]. DNA hydrogels, which are constructed through crosslinking of DNA molecules, are particularly useful for drug delivery systems due to their inherent porosity, biocompatibility, and the ability to engineer DNA sequences for specific functions [25]. Additionally, DNA-based hydrogels are employed in biosensing applications, offering a cost-effective, programmable, and highly sensitive platform for detecting various compounds. For example, biosensor designs may incorporate a synthetic polymer scaffold combined with functional DNA cross-linkers to detect target substances, with detection reported through various mechanisms [25, 26].

3. Different Types of Biopolymer-Hydrogels

There are many different biopolymer-based hydrogels, but the main ones include pH-sensitive gels, temperature-sensitive gels, electrosensitive gels, and light-responsive gels.

3.1 pH-Sensitive Hydrogels

pH-sensitive hydrogels are engineered to respond dynamically to variations in environmental pH, a characteristic achieved by incorporating acidic or basic functional groups into their polymer structures [27]. These hydrogels often exhibit amphiphilic properties, containing both acidic and basic groups that enable them to undergo significant phase transitions in response to changes in pH. In an acidic or basic environment, these hydrogels can exhibit a two-phase transition: the first phase involves the formation of a gel-like network through polymer-polymer interactions, characterised by pronounced hydrophobicity. This interaction leads to the hydrogel's contraction and a decrease in its volume. Conversely, the second phase is marked by interactions between the solvent and the polymer, creating a mixed phase wherein the hydrogel swells as it becomes more hydrophilic [28]. This dual-phase behaviour allows for the fine-tuning of hydrogel properties based on the surrounding pH, making them suitable for applications requiring precise control over swelling and deswelling dynamics.

3.2 Thermogels

Thermoresponsive hydrogels, or thermogels, are designed to change their physical state in response to temperature fluctuations. These hydrogels typically incorporate methyl, ethyl, and propyl groups that interact with water molecules through hydrogen bonding, which is temperature-dependent [29]. As the temperature varies, these hydrogen bonds alter, leading to changes in the hydrogel’s swelling behaviour. Most thermogels increase in water solubility with rising temperatures; however, certain polymers exhibit the opposite behaviour, characterised by a phase transition at a specific temperature known as the "lower critical solution temperature" (LCST) [29]. In positive thermosensitive hydrogels, increased temperature results in reduced solubility, whereas negative thermosensitive hydrogels display increased solubility with rising temperatures. The LCST can be modulated by incorporating hydrophilic components, which is beneficial for drug delivery systems. Poly(N-isopropylacrylamide) (PNIPAM) is one of the most extensively studied thermoresponsive hydrogels in tissue engineering. Other examples include collagen, agarose, hyaluronic acid, poly(organophosphazenes), and chitosan [30, 31]. Thermogels are also advantageous in reducing the critical micelle concentration (CMC), facilitating the formation of micelles for drug delivery and improving their stability, which enhances the efficiency of drug targeting and delivery [32].

3.3 Electro-Sensitive Hydrogels

Electrosensitive hydrogels are designed to respond to electric fields, exhibiting swelling or contraction in the presence of an electric current. These hydrogels are composed of polyelectrolytes that generate counterions and immobile charged groups

upon exposure to an electric field, resulting in localized swelling or shrinkage at the anode and cathode. This electro-responsive behaviour leads to bending or deformation of the hydrogel, which depends on factors such as the hydrogel's structural composition, the strength and orientation of the electric field, and the duration of exposure [33, 34]. Hydrogels incorporating acrylamide and carboxylic acid derivatives have been successfully employed as electro-sensitive and biocompatible smart materials, with applications spanning sound dampening, chemical separations, and controlled drug delivery [35]. The increasing interest in electrosensitive hydrogels is driven by their potential use in advanced biosensors and functional tissue-engineered scaffolds and implants. When combined with 3D printing technologies, these hydrogels represent a cutting-edge approach to biomedical applications [36].

3.4 Light-Sensitive Hydrogels

Light-sensitive hydrogels possess the remarkable ability to alter their physical properties in response to exposure to specific wavelengths of light [37]. This photoreactivity is primarily mediated by chromophores, which are light-responsive functional groups embedded within the hydrogel matrix. Upon irradiation, these chromophores trigger changes such as the expansion or contraction of the gel, making these materials highly versatile for applications that require remote and non-invasive control. Beyond their direct response to light, these hydrogels may also exhibit sensitivity to pH variations, further broadening their potential utility [37]. In certain instances, functional groups within the hydrogel are designed to be heat-sensitive, where the absorption of light at specific wavelengths induces localised heating, leading to a thermal response and subsequent structural changes in the gel [37]. This dual responsiveness to both light and heat significantly enhances the functionality of these hydrogels in sophisticated biomedical and industrial applications.

3.5 Shape-Changing Hydrogels

Shape-changing hydrogels represent a frontier in smart material design, engineered to undergo dramatic alterations in form when exposed to external stimuli such as pH shifts, temperature fluctuations, or the introduction of aqueous solutes. The unique ability of these materials to undergo controlled, reversible shape transformations is rooted in the differential swelling behaviour of distinct regions within the hydrogel structure. These hydrogels are often initially fabricated as flat films, which can autonomously fold or roll into complex geometries such as tubes or other three-dimensional shapes in response to the stimuli [38]. This capacity for shape morphing is particularly valuable in biomedical applications, especially in the context of cell implantation and tissue engineering. For instance, during the implantation of bone marrow cells, a shape-changing hydrogel can transition into a tubular form within the bone cavity, maximising the surface area for cell contact and proliferation, thereby accelerating the delivery and integration of therapeutic cells [38]. The versatility and precision of shape-changing hydrogels position them as a cutting-edge innovation in the development of next-generation biomedical devices and therapeutic systems.

4. Fabrication Methods

4.1 Creating Hydrogels

The fabrication of hydrogels is a sophisticated process that draws upon an extensive array of chemical reagents and precise methodologies, each tailored to achieve specific material characteristics. For instance, in the synthesis of injectable high-strength hydrogels, a complex blend of compounds such as ethylene oxide, potassium, naphthalene, diphenyl methane, pentaerythritol, and anhydrous dimethylsulfoxide (DMSO) are meticulously selected for their chemical compatibility and functional properties [39]. These reagents are introduced into a reactor, where they are subjected to rigorous mixing under carefully controlled stirring rates and temperatures, ensuring a uniform reaction environment [40]. The resultant solution, formed through this meticulous process, is then combined with additional pre-formulated solutions, each contributing to the final material's high-strength characteristics. This hydrogel, thus produced, is endowed with the mechanical robustness necessary to withstand the significant biomechanical forces encountered in applications such as cartilage tissue repair.

4.2 Printing Hydrogels

The integration of 3D printing technology into the realm of hydrogel fabrication marks a significant leap forward in the field of biomaterials, particularly in biomedical engineering. This technology enables the precise construction of biodegradable hydrogels, engineered to perform critical functions within biological systems, such as the formation of extracellular matrices and the creation of intricate vasculature networks. The inherent versatility of 3D printing allows for the meticulous design of hydrogel scaffolds that can swell in aqueous environments while maintaining a delicate balance between flexibility and rigidity through tailored polymer crosslinking [41]. This ability to fine-tune the structural and mechanical properties of hydrogels ensures that they are optimally suited for their intended biomedical applications, whether it be in tissue engineering, regenerative medicine, or drug delivery systems [42]. The precision afforded by 3D printing also facilitates the customisation of hydrogels, allowing researchers to adapt the material properties to meet the specific demands of each application, thus pushing the boundaries of what can be achieved with hydrogel-based technologies.

4.3. Physical Crosslinking

Crosslinking serves as a pivotal technique in the engineering of hydrogels, fundamentally altering their structural integrity and functional capabilities. By establishing micro-level polymeric connections within the gel matrix, crosslinking can dramatically enhance the mechanical strength of the hydrogel, making it more resilient and durable [43]. However, the utility of crosslinking extends far beyond mere mechanical reinforcement. This process can be harnessed to imbue hydrogels with bespoke functionalities, such as the introduction of reactive sites that facilitate specific

biochemical interactions within the material. For example, in a biomedical context, crosslinking can be used to incorporate signalling cues that guide the hydrogel's behaviour in situ, such as promoting adhesion at targeted injection sites or enabling the controlled release of therapeutic agents [44]. Crosslinking methods are diverse, encompassing both chemical and physical approaches [45]. Chemical crosslinking might involve robust bonding techniques like imine bonding, metal complexation, or disulfide bond formation, each contributing to a tightly-knit gel structure with enhanced stability. On the other hand, physical crosslinking methods, such as hydrogen bonding and host-guest interactions, offer a more delicate approach, allowing for the creation of hydrogels that balance strength with flexibility and responsiveness [44, 45]. These versatile crosslinking strategies enable the development of hydrogels that are not only structurally sound but also highly functional, capable of meeting the diverse challenges posed by advanced biomedical applications.

5. Applications

5.1 Cell Delivery for Tissue Regeneration

The diverse and intricate fabrication methods employed in the creation of biopolymer-based materials underscore their critical role in advancing biomedical applications. Collagen, a fundamental polypeptide, is typically fabricated through demineralisation processes, making it an ideal candidate for drug delivery, tissue engineering, and implant development, owing to its inherent biocompatibility and structural properties [46]. Similarly, gelatin, another polypeptide, is derived by boiling natural sources, a process that preserves its utility in drug delivery and tissue engineering, where its biodegradability and capacity for controlled drug release are particularly advantageous [47]. Elastin, distinguished by its elasticity, is synthesised through the polymerisation of tropoelastin monomers, a technique that enables the production of robust scaffolds for tissue engineering, replicating the dynamic mechanical properties of natural tissues [48].

In the domain of polysaccharides, alginate is extracted from the cell walls of algae, a method that exploits its gelation capabilities for cell delivery applications, where it serves as a biocompatible matrix for encapsulating and transporting therapeutic cells [49]. Cellulose, another polysaccharide, is produced via the extrusion of dissolved natural materials such as wood pulp, and its application spans biomedical devices, tissue engineering, and drug delivery, thanks to its mechanical strength and ease of modification [50]. Glycosaminoglycans, synthesised through the creation of UDP-derived activated sugars, are essential for tissue engineering, where their ability to mimic the extracellular matrix enhances cellular adhesion and proliferation [51]. Finally, DNA, classified under nucleic acids, is fabricated through light-directed combinatorial chemical synthesis, a sophisticated method that allows for its use in drug delivery, tissue engineering, cancer therapeutics, and biosensing. The programmability and precision afforded by this fabrication technique make DNA-based materials uniquely suited to these advanced biomedical applications, offering unparalleled specificity and functionality [52].

5.2 In Cancer therapy

Hydrogels represent a promising advancement in the field of cancer therapy by facilitating the localized and controlled release of anticancer drugs, thereby minimizing off-target effects and enhancing therapeutic efficacy. Thermo-responsive hydrogels have demonstrated particular promise in this regard, as they are capable of undergoing phase transitions at specific temperatures, which in turn modulates drug loading and release dynamics. A notable example is the chitosan/Disulfiram (DSF)-loaded hydrogel, which exhibited superior cellular uptake compared to DSF alone, while also providing sustained drug delivery, a crucial factor in enhancing the therapeutic impact of cancer treatment [53, 54]. Further illustrating the potential of hydrogel systems in cancer therapy is the chitosan-based hydrogel neutralized with beta-glycerophosphate, engineered to deliver the anti-cancer drug paclitaxel. This system showcased its capacity for localized drug release, with only 32% of the loaded drug being released by day 17, resulting in significant inhibition of tumor growth, thus underlining the hydrogel's potential to improve treatment outcomes [55]. In another study, a hydrogel composed of gelatin seeded with adipose-derived stem cells was explored for its potential in breast cancer treatment. The hydrogel was found to effectively mimic the physical and chemical properties of the extracellular matrix (ECM) of adipose tissue, maintaining its structural integrity for approximately 21 days in vitro. This scaffold not only exhibited mechanical properties akin to breast tissue but also holds promise as a sustainable option for future breast cancer therapies [56]. Moreover, a mucin glycoprotein-based hydrogel, designed to simultaneously deliver the hydrophobic drug paclitaxel and the hydrophilic drug polymyxin B, demonstrated the capacity to sustainably release both drugs over more than four weeks. This dual-drug release mechanism not only reduced the viability of HeLa epithelial cancer cells but also prevented bacterial growth, showcasing the hydrogel's multifaceted therapeutic potential [57].

The precision with which these hydrogel systems deliver drugs to targeted locations greatly enhances drug efficacy while mitigating the risk of adverse effects on healthy tissues and organs. However, the complexity of cancer as a disease, coupled with the necessity for aggressive treatment regimens, means that progress in this area has been slower than anticipated. Nonetheless, ongoing research and future studies, particularly those involving cancer patients, are essential to fully realize the potential of hydrogels in providing more effective and targeted cancer therapies.

Conclusion

Hydrogels, a distinctive class of polymeric materials, are notable for their intricate hydrophilic chain networks, which confer the remarkable ability to absorb and retain substantial volumes of water within their interstitial matrices. The versatility of biopolymers, particularly, renders them indispensable in the engineering of hydrogels tailored for specialised applications, capitalising on their unique physicochemical properties. An extensive array of biopolymers, encompassing saccharides, peptides, and even nucleic acids, can be adeptly manipulated to form hydrogels, each selected for its intrinsic benefits aligned with specific functional demands.

Polypeptide-based hydrogels, such as those derived from collagen, gelatin, and elastin, exemplify the confluence of biocompatibility and structural integrity, making them prime candidates for biomedical applications. In parallel, polysaccharide-derived hydrogels, including those formulated from alginate, cellulose, and glycosaminoglycans, offer a suite of properties such as biodegradability and low immunogenicity, which are pivotal in therapeutic contexts. Moreover, the incorporation of nucleic acids into hydrogel structures heralds a new frontier in the design of smart biomaterials, capable of dynamic responsiveness to biological stimuli. Recent advances in hydrogel technology have seen the emergence of sophisticated constructs, such as dual-stimuli responsive hydrogels that amalgamate distinct polymer networks. These innovative materials can be engineered to form complex architectures, such as tubular structures, specifically designed to facilitate vascular regeneration. The development of double-network hydrogels, characterised by their heterogeneous cross-linking densities, marks a significant leap forward in material science. These hydrogels exhibit exceptional mechanical resilience, with the capacity to endure both shear and tensile stresses, making them particularly suitable for applications in ligament repair and other load-bearing tissues. The synthesis of hydrogels can be approached through a variety of methodologies, ranging from conventional chemical synthesis to state-of-the-art additive manufacturing techniques like 3D printing. These fabrication processes not only enhance the structural precision of hydrogels but also expand their functional versatility. The application of hydrogels in tissue engineering and regenerative medicine is especially promising, as these materials can be engineered to deliver therapeutic agents, such as insulin or chemotherapeutic drugs, in a controlled and localised manner, thereby maximising therapeutic efficacy while minimising systemic side effects. Since 2015, the application of hydrogels within the biomedical landscape has catalysed a paradigm shift, leading to the exploration of their potential in encapsulating and delivering a diverse array of bioactive compounds, including drugs, cells, and genetic material. The ongoing evolution of hydrogel technology promises to unlock new possibilities in the development of bespoke therapeutic platforms, heralding a new era in the intersection of materials science and medicine.

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