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Review Article

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A Smart Material in Nanotechnology and Bioengineering: Nanogels

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Abstract

Nanogels are chemically or physically crosslinked three-dimensional hydrophilic polymer networks. Due to their relatively high drug encapsulation capacities, large surface areas, homogeneity, adjustable sizes, ease of preparation, minimal toxicity, and stability, they are promising and innovative materials for next-generation drug delivery systems. They can be prepared with natural or synthetic polymers, and polysaccharides are attractive and promising biomaterials for nanogel preparation due to their abundance in nature and low cost. Their ability to be prepared in response to environmental stimuli, such as temperature, pH, ionic strength, electric, and magnetic fields, significantly enhances their potential. Moreover, these nanogels have potential as nanomaterials for various biomedical applications, including cancer treatment, anti-inflammatory therapy, drug delivery systems, biological imaging, detection of bioactive small molecules, cell behavior analysis, three-dimensional cell culture, bone tissue regeneration, wound /healing, and more. This review provides a brief overview of nanogels in general, nanogel synthesis, release mechanism, polysaccharide-based nanogels and their development in potential application areas.

Keywords: Crosslinking, Nanogel, Nanocarrier, Polymer, Polysaccharide

Introduction

Nanoscience studies the unique properties of materials in the range of 1-100 nm, while nanotechnology enables the production of nanomaterials that can improve treatment processes by offering safer and smarter products in the healthcare sector, utilizing these properties (1). In recent years, one of these nanomaterials, nanogels, has emerged as a promising innovative drug delivery system. Their high drug encapsulation capacities, adjustable sizes, ease of preparation, minimal toxicity, and sensitivity to external stimuli make them a potential tool for a wide range of applications (2,3). The careful selection of polymers during the preparation of these nanogels and the resulting architectural versatility allow them to encapsulate and deliver a wide range of hydrophilic and lipophilic molecules, from inorganic compounds to biomolecules such as amino acids, proteins, and nucleic acids (DNA, RNA) without compromising their gel-like behavior (4). The selected polymers can be natural, semi-synthetic, or synthetic, and nanogels can be formed through the crosslinking of polymer chains (5). Natural polymers are generally non-toxic, biocompatible, and biodegradable. Polysaccharides are commonly used natural polymers in nanogel synthesis due to their reactive functional groups. Furthermore, because they can be degraded by bacterial enzymes, they appear to be promising polymers for the preparation of nanoscale drug delivery systems (6). Therefore, nanogels prepared from polysaccharides, a

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natural polymer, have become an important nanocarrier for the delivery of a wide variety of molecular and macromolecular therapeutics since their discovery (7,8).

Several strategies have been proposed to adjust the physical, chemical, and mechanical properties of polysaccharide-based nanogels, and new production methods and application areas have become the focus of various studies. The aim of this review is to examine current research on polysaccharide-based nanogels and provide an overview of their potential applications.

Nanogels

Nanogels are crosslinked polymer networks that swell in a suitable solvent (Figure 1). They are typically characterized by a spherical shape, but depending on the production methods, other shapes are also possible (4). These structures, in addition to their water absorption capacities, possess properties such as high surface area, adjustable sizes, rapid and controlled water uptake, high biocompatibility, and flexibility (9). Due to their adaptability, their physicochemical properties can be finely controlled, which significantly alters the effects exhibited by the nanogels (10). For example, the size-dependent effects of nanogels primarily stem from the increased surface area-to-volume ratio as the particle size decreases. A larger surface area means more exposed atoms or molecules, which results in enhanced surface reactivity (11). While size is an important factor, it is also important to note that other parameters, such as shape, composition, and surface chemistry, can influence the physical and chemical properties of nanogels.

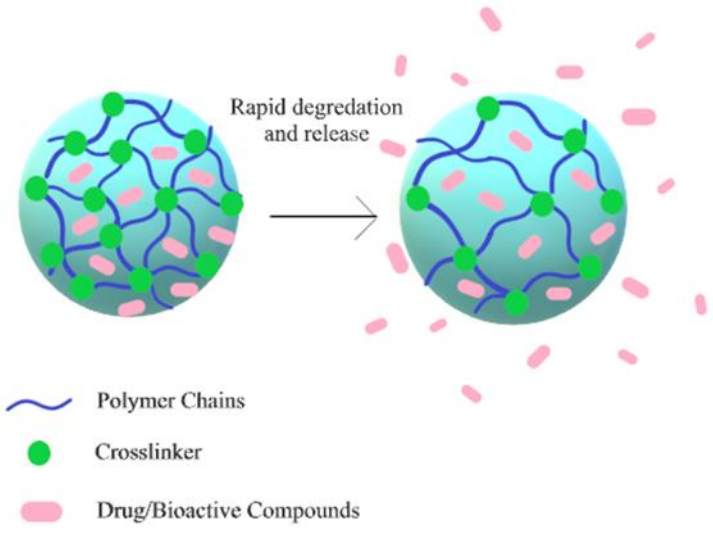

Figure 1. Schematic representation of the swelling of the nanogel network in a solvent.

Another key feature that represents a turning point in nanogel design is their sensitivity to external environmental factors such as pH, ionic strength, enzymes, and temperature. These structures, which can change their physical and chemical properties in response to environmental factors, have significant applications in sensors, drug delivery systems, tissue engineering, and biomedical engineering (12). They can trigger drug release in specific areas of the body, making

treatment processes more effective and targeted. Therefore, externally responsive nanogels are particularly of interest in bioactive agent/drug delivery applications.

Nanogels can be synthesized using natural or synthetic polymers through chemical or physical crosslinking (5). Commonly used natural polymers for nanogel synthesis include dextran, chitosan, heparin, hyaluronic acid, and alginate, while synthetic polymers include poly(methyl methacrylate), poly(D,L-lactic acid), poly(glycolic acid), poly(D,L-lactic-co-glycolic acid), and poly(ε-caprolactone) (13). The high liquid absorption capacity of nanogels is related to the presence of hydrophilic functional groups in the polymer structures, such as –OH, –CONH–, –$CONH_2$–, and –SO_3H (3). The diversity of polymer systems and the simple modification of their physicochemical properties help overcome the limitations encountered in transporting agents with low solubility and stability, facilitating the preparation of multifunctional nanogel systems (14,15).

Nanogel Synthesis Methods

There has been significant interest in developing easy, fast, and effective strategies for the preparation of nanogels. Nanogels can be synthesized by simultaneously performing polymerization and crosslinking processes. Since most of the monomers and crosslinking agents used in the preparation of these nanogels are water-soluble, polymerization reactions are typically conducted in an aqueous environment. Alternatively, these processes can be performed separately: first, the polymers are formed, and then crosslinking can occur between the polymer molecular chains to produce the nanogels. This method is particularly suitable for preparing nanogels based on natural polymers (16).

Nanogels can be synthesized through various methods, including emulsion polymerization, nanoprecipitation, emulsion-solvent evaporation, radical polymerization, and photo-induced crosslinking (4). Traditionally, the synthesized nanogels are classified into physical or chemical crosslinked nanogels based on the type of crosslinking (17). Chemical crosslinking results in the formation of intermolecular or intramolecular covalent bonds within the nanogels (18). Crosslinkers such as diepoxy compounds, genipin, glutaraldehyde or diphenylphosphoryl chloride are used to establish covalent bonds between polymers. In nanogels, these bonds are usually strong and permanent, which increases the stability of the structures. They are formed by incorporating reactive functional groups into low molecular weight monomers or macromolecular precursors, allowing the structure and properties of the gel particles to be tuned. Nanogels formed through chemical cross-linking have colloidal stability under in vivo conditions, which is necessary for the controlled release of drugs induced by undesirable dissociation of the gel network (19). In contrast, physically crosslinked nanogels are formed by relatively weak interactions such as hydrogen bonding, electrostatic, hydrophobic, or ionic interactions and are less stable than chemically crosslinked nanogels (3). This stability is influenced by factors such as the size of the particles, the nature of the polymer matrix and its chemical composition, and the type of crosslinking used for the polymer chains.

Nanogels exhibit significant swelling capacity in aqueous environments. The key point that prevents dissolution and maintains structural integrity is the crosslinkers, which form a network structure by linking polymer chains together (20). With a higher concentration of crosslinkers,

gels tend to have shorter polymer chains and show less swelling in the same solvent (21). Nanogels swell by absorbing the solvent, and due to the crosslinked polymeric network structure, they do not dissolve and retain their structural integrity (22). Their inability to dissolve ensures the mechanical stability of nanogels, thereby enhancing the long-term effectiveness of drug delivery systems.

Important factors to consider in the synthesis of nanogels include colloidal stability, increased loading capacity, enhanced surface area, biodegradability, biocompatibility, and the release of therapeutic agents. The desired properties and the intended application influence the selection of the synthesis approach for nanogels.

Release Mechanisms of Nanogels

Nanogels play a significant role as delivery systems due to their water solubility, biocompatibility, biodegradability, as well as their encapsulation stability and smart release properties (23). The release of biomolecules or small molecules depends on the properties of the polymers used in the preparation of the nanogels. Typically, hydrophobic biomolecules, which are unstable and difficult to deliver, can be placed in the porous networks of nanogels to improve their stability, circulation, and therapeutic efficacy. The network size of the nanogel matrix plays an important role in sustaining the release, which can occur either through simple diffusion from the matrix system or via external stimuli. The basic release mechanisms of biological agents include diffusion, erosion of nanogel matrices, changes in surrounding pH, displacement with counterions in the environment, and release mechanisms triggered by external stimuli such as magnetic fields, temparature and light (24). Under these stimuli, nanogels undergo physicochemical changes such as swelling, contraction, polymer chain degradation, and dissociation, leading to drug release. Physical degradation involves the swelling and shrinking of polymers that are sensitive to environmental conditions, while chemical degradation leads to the breakdown of the nanogel structure through the dissolution of cross-links or enzymatic degradation (25). These chemical changes trigger drug release, contributing to therapeutic effects. Additionally, biological degradation occurs through the metabolism of nanogels in the body or their phagocytosis by immune cells. A thorough understanding of these swelling and degradation properties of nanogels is crucial for the development of controlled drug release and targeted therapy strategies, leading to enhanced therapeutic efficacy and better therapeutic outcomes (26).

Polysaccharide-Based Nanogels

Today, polysaccharide-based nanogels are of interest as carriers for various bioactive agents such as drugs, due to their biocompatibility, physicochemical properties, and unique multifunctional groups (7,27,28). Polysaccharides are biologically degradable polymers and typically consist of several monosaccharide units linked by glycosidic bonds. Due to their abundant presence in nature, low processing cost, non-toxicity, water solubility, and bioactivity, polysaccharides are among the most attractive and promising polymers in the field of nanomedicine. These polymers can exhibit behaviors such as volume change, swelling, or contraction in response to external stimuli. The most common method for synthesizing polysaccharide-based nanogels involves covalent crosslinking, which forms covalent bonds between polysaccharide chains (29). Covalent

crosslinking offers specific advantages in regulating the nanogel's strength, structure, and swelling behavior, which are crucial for controlled loading and programmed release of therapeutic and theranostic agents (27).

Polysaccharide-based nanogels can be designed to encapsulate a variety of therapeutic substances, including small molecule drugs (both hydrophobic and hydrophilic), proteins/peptides, nucleic acids, and vaccines. For biotherapeutic delivery, the potential of polysaccharide-based nanogels lies in their ability to maintain bioactivity and achieve sustained and/or controlled drug release, thereby reducing the need for frequent applications (30). Commonly used polysaccharides in nanogel production include starch, cellulose, dextran, chitosan, xanthan gum, and pectin.

Starch is a flexible polysaccharide used for drug and bioactive delivery systems due to its biodegradability and biocompatibility. Natural starch nanogels with nanometer-sized dimensions have been studied for versatile applications in biomedical, food, and pharmaceutical industries (28). Starch's ability to crosslink with various chemical crosslinkers makes it easy and fast to obtain nanogels.

Chitosan is similarly used as a drug delivery system, where it helps to improve the bioavailability and stability of drugs while also being effective in reducing toxicity. Additionally, due to its antimicrobial, anti-inflammatory properties and its capacity to support tissue regeneration, chitosan is also used in wound healing and tissue engineering (31). Common methods for preparing chitosan nanogels include reverse microemulsion, water-oil heterogeneous gelation, and aqueous homogeneous gelation techniques (32).

Cellulose, another polysaccharide, is abundant in nature and is known for its renewability, biodegradability, biocompatibility, and environmental friendliness. Cellulose and its derivatives are excellent polymers for gel production. Chemical and/or physical crosslinking can be applied during the preparation of nanogels, especially considering the properties of cellulose copolymers. Depending on their characteristics, these nanogels find applications in many different fields (33).

Polysaccharide-Based Nanogels Application Areas

The emergence of nanotechnology in medicine has facilitated the development of potential therapies and diagnostic methods for various diseases and disorders. Polysaccharide-based nanogels are used for the encapsulation and controlled release of various functional molecules, including drugs, proteins, and genetic materials, offering unique advantages such as biodegradability, biocompatibility, and adjustable properties (34). In the literature, it is noted that polysaccharides like chitosan, hyaluronic acid, starch, alginate, dextran, and cellulose have been used as drug delivery systems, leading to impressive therapeutic outcomes. Polysaccharide-based nanogels exploit the properties of biopolymers to increase intracellular penetration, ensure the stability of encapsulated biomolecules, and reduce early drug degradation rates. Additionally, the effectiveness of polysaccharide-based nanogels depends on the characteristics of the polysaccharides and the preparation parameters.

For instance, the type of starch, the gelation time, and the amylose/amylopectin ratio have been identified as critical parameters during the synthesis of starch nanogels (6,28). Numerous starch

derivatives and combinations of starch with various polymers can facilitate the synthesis of nanogels with desired properties. Starch nanogels serve as ideal carriers in biomedical applications, including drug and peptide delivery, and are particularly suitable for oral administration (6).

Chitosan nanogels, with their high biocompatibility, biodegradability, pH sensitivity, mucoadhesive properties, and thermosensitivity, have become versatile ideal drug delivery systems. The amine groups in chitosan act as reactive sites during nanogel synthesis. The ability to modify chitosan provides opportunities to create new nanogels that can be used in nearly all biomedical fields, including wound dressing, cancer suppression, tissue engineering, and biological imaging (35, 36).

Similarly, other polysaccharide-based nanogels are highly useful as carriers for a wide range of active compounds due to their physicochemical and biological properties. Polysaccharides possess unique properties, such as the ability to mimic the microenvironment of natural extracellular matrices, which is highly investigated for use in bioengineering applications. Furthermore, polysaccharides or their derivatives, when used to form nanogels, can be combined with other polymers to reach various targets (30). Therefore, nanogels are prepared from a wide range of synthetic and natural biopolymers, encapsulating small molecules or biomacromolecules through the pores of the three-dimensional network. The three-dimensional polymer network of nanogels, produced via chemical or physical crosslinking, can encapsulate hydrophilic or hydrophobic molecules, including drugs, proteins, genetic material patterns, and even small nanoparticles. Recent significant advances in the synthesis of polysaccharide-based nanogels have enabled the adaptation of nanogels with specific properties by providing access to complex architectures and compositions.

Conclusion and Future Perspective

Recently, there has been significant interest in nanocarriers within the field of drug delivery systems research. One such nanocarrier, nanogels, has attracted attention due to their customizable structures, which can be tailored to transport charged bioactive agents to desired target areas. Nanogels are an intriguing type of hydrophilic polymeric network, exhibiting good biocompatibility, high water absorption, and stability, while also demonstrating minimal toxicity for drug loading applications. Notably, polysaccharide-based nanogels form a class of carriers that are easy to produce, versatile, and economically feasible. These nanogels possess multifaceted properties, enabling the effective delivery of biologically active molecules, particularly biopharmaceuticals.

The synthesis of nanogels can be achieved through various methods, and the choice of method significantly influences the final characteristics of the resulting nanogel. Overall, polysaccharide-based nanogels show great potential in advancing biomedical and pharmaceutical fields. As discussed in this review, the design and development of functional and sensitive nanogels represents an important breakthrough in the safe and effective delivery of bioactive molecules. These aspects make them fascinating as soft model systems for fundamental research and particularly for a wide range of biological applications.

Compliance with Ethical Standard

Conflict of interests: The author declares that for this article they have no actual, potential, or perceived conflict of interests.

Ethics committee approval: The author declares that this study does not include any experiments with human or animal subjects; therefore, no ethics committee approval is needed.

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