

Construction Strategies and Application Research of Polysaccharide-Nanoparticle Composite Delivery Systems

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Abstract. Background: Polysaccharides exhibit multiple biological activities and are used as delivery systems due to their molecular designability, degradability, and targeting properties. However, their high molecular weight, poor water solubility, and instability pose bottlenecks to their application. The addition of nanoparticles can improve the functions of polysaccharide delivery systems, but there are relatively few summary articles on polysaccharide-nanoparticle composite delivery systems and their construction strategies. Methods: This paper evaluates relevant articles on polysaccharides, nanoparticles, and their composite delivery systems. The search focused on keywords closely related to the theme, such as "chitosan", "hyaluronic acid", "nanoparticles", "construction strategies", "targeting", etc. The search process was carried out using databases such as Web of Science, Google Scholar, and PubMed. Results: The construction and application of polysaccharide-nanoparticle composite delivery systems were discussed from the aspects of raw materials, construction strategies, functions and advantages, applications, etc. Conclusions: Polysaccharide-nanoparticle composite delivery systems have synergistic effects compared with single delivery systems, which helps to enhance the efficacy of the delivery system and is of great significance for promoting the application of polysaccharide-nanoparticle composite systems in various delivery scenarios.

Keywords: polysaccharides, nanoparticles, drug delivery, construction strategies, application fields.

1. Introduction

Polysaccharides, as extremely important components of plant and animal cell membranes and microbial epidermal cells, possess outstanding biological functions [1]. In terms of immune homeostasis, Elvira et al. demonstrated that milk-derived oligosaccharides can increase the secretion of intestinal secretory immunoglobulin in a dose-dependent manner, confirming their role in promoting immune development [2]. Regarding oxidative stress regulation, Michaowoczkowski's team found that high-molecular-weight oat β -glucan can significantly increase the glutathione/oxidized glutathione ratio in the body of patients with 2,4,6-trinitrobenzene sulfonic acid-induced colitis, maintaining the redox homeostasis of the reproductive system [3].

Polysaccharides have attracted much attention as biological delivery carriers in recent years, with three major advantages: designability, degradability, and targeting. The structural designability of polysaccharides as delivery carriers stems from their flexible modifiable properties: sulfation modification enhances biological activity by introducing sulfonic acid groups, while carboxymethylation modification significantly improves water solubility and biocompatibility through hydroxyl substitution [4]. The natural degradability of polysaccharides not only avoids the potential biological accumulation risk of traditional synthetic carriers but also facilitates the precise release of drugs. For example, Bacteroidetes can directionally cleave polysaccharide glycosidic bonds and generate biocompatible products through the enzyme hydrolysis mechanism mediated by polysaccharide utilization sites [5]. The targeting mechanism of polysaccharides integrates the advantages of ligand recognition and designability. Hyaluronic acid nanoparticles can significantly improve the intracellular enrichment efficiency of drugs and the effect of precise treatment of various cancers by specifically binding to cluster of differentiation (CD44) receptors (overexpressed on the surface of tumor cells such as breast cancer) [6].

Although polysaccharide-based delivery systems show broad application prospects due to their biocompatibility, modifiability, and targeting properties, their clinical transformation still faces three

key bottlenecks. First, polysaccharides have insufficient water solubility. For example, chitosan exhibits hydrophobic properties due to the deprotonation of amino groups in neutral/alkaline environments, making it insoluble in aqueous and organic solvents, which easily leads to aggregation and precipitation in body fluids, affecting efficacy and safety [7]. Second, polysaccharides can easily damage biological barriers. Take lipopolysaccharide as an example, it can cause the loss of dopaminergic neurons in the substantia nigra region by increasing the permeability of the blood-brain barrier [8]. Therefore, it is urgent to introduce synergistic strategies to collaboratively optimize the physicochemical properties and biological functions of biological polysaccharide carrier systems.

Nano-delivery systems have significant advantages in delivery systems. For example, loading the hydrophobic drug paclitaxel into the hydrophobic core region of a nano-carrier can increase its solubility by 1-2 orders of magnitude, enhancing the antitumor effect while significantly reducing systemic toxicity [9]. In addition, polyethylene glycol-modified chitosan oligosaccharide-arachidic acid-based nanoparticles containing doxorubicin (DOX) have a drug half-life that is significantly increased by 899.82% compared with the free DOX group, prolonging the circulation time of the drug in the bloodstream [10].

The synergistic system of polysaccharides and nanomaterials can effectively break through the bottleneck of drug delivery through structural and functional integration. In terms of targeting enhancement, CS-hyaluronic acid double-modified nanoparticles can reduce the half-maximal inhibitory concentration of breast cancer cells by 3-5 times through a dual targeting mechanism of pH response and CD44 receptor-mediated, significantly enhancing the tumor-selective killing effect of docetaxel [11]; in the field of barrier repair, Eucommia polysaccharide-modified nano-selenium can effectively alleviate 3% dextran sulfate sodium-induced colitis by enhancing intestinal mucosal barrier function and antioxidant capacity [12].

This review mainly explains the synergistic mechanism of nanoparticles and polysaccharide carriers, focusing on the latest research progress in bioactivity enhancement and intelligent drug release, so as to provide references and research ideas for the application of nano-polysaccharide delivery systems in the biomedical field.

2. Construction Strategies of Nanoparticle-Polysaccharide Composite Systems

2.1 Types of Polysaccharides

2.1.1 Natural Polysaccharides

Natural polysaccharides occupy a core position in the construction of nanoparticle-polysaccharide composite delivery systems due to their source diversity and functional plasticity. Alginate, an anionic polysaccharide extracted from the cell wall of brown algae, forms a protective gel barrier in the gastric acid environment through its pH-sensitive gelation property, escorts the contents to the intestinal alkaline environment, and then disintegrates and releases the drug in a targeted manner. It can also form a three-dimensional network structure with calcium ions to precisely regulate the sustained-release period of protein drugs [13].

2.1.2 Chemically Modified Polysaccharides

Chemically modified polysaccharides can break through the functional limitations of natural polysaccharides through structural optimization. Sulfated polysaccharides introduce sulfonic acid groups (-SO₃H) into the polysaccharide chain through sulfonation reaction, forming strong polyanionic properties, which not only significantly improves the drug loading efficiency of cationic drugs but also endows them with anticoagulant activity, showing unique potential in cardiovascular targeted delivery [14];

2.1.3 Microbe-Derived Polysaccharides

Microbe-derived polysaccharides are known for their high fermentation efficiency and stability. For example, xanthan gum, obtained by fermenting *Xanthomonas campestris*, is a high-molecular-

weight water-soluble polymer. Its low-concentration high-viscosity property and broad pH/temperature tolerance can significantly improve the stability and adhesion of drug-loading systems, especially suitable for the adhesion-controlled release of oral sustained-release preparations or local patches [15].

2.2 Types of Nanoparticles

2.2.1 Lipid-Based Nanoparticles (NPs)

Lipid-based nanoparticles (NPs) are a class of highly valuable nanocarriers, usually composed of a phospholipid bilayer wrapping a water core. This structure enables them to load both hydrophilic drugs (stored in the water core) and hydrophobic drugs (embedded in the lipid layer), showing strong drug-loading capacity. In addition, NPs usually have good biocompatibility, and their surfaces are easy to be functionalized to meet different application requirements. Based on these characteristics, NPs have a wide range of application prospects in the fields of drug delivery and biomedicine [16].

2.2.2 Inorganic Nanoparticles

Inorganic nanoparticles, as an important branch of the nanomaterial field, have unique physical and chemical properties, mainly including the following types:

Gold nanoparticles (AuNPs) are made of elemental gold through a chemical reduction method and have diverse morphologies (such as spherical, rod-shaped, star-shaped, etc.). AuNPs can effectively absorb light energy and convert it into heat under near-infrared light irradiation. Photothermal therapy can kill 95% of cancer cells treated with AuNPs. In addition, due to the chemical inertness of gold elements, AuNPs are not easy to trigger immune reactions, so they have attracted much attention from researchers in the field of biomedical treatment [17].

Magnetic nanoparticles (MNPs) are composed of metals such as iron, cobalt, nickel, or their oxides and exhibit superparamagnetism, that is, they have no magnetism in the absence of an external magnetic field and can be strongly magnetized in the presence of an external magnetic field. Using this characteristic, people can accurately control their relative position in the human body through an external magnetic field. Based on this, MNPs have important application prospects in biomedical fields such as magnetic resonance imaging and targeted drug delivery [18].

2.2.3 Biomimetic Nanoparticles

Biomimetic nanoparticles are composed of an artificially synthesized nano-core (such as silica, gold) and a natural biological material shell (such as cell membrane, exosome). Studies have shown that nanoparticles coated with red blood cell membranes can escape the recognition of the immune system and significantly prolong the circulation half-life [19]; The application of exosomes can overcome the problems of reduced targeting efficiency and tissue penetration of nanoparticles, which has been confirmed to improve the accuracy and precision of cancer treatment and minimize potential side effects [20].

2.2.4 Stimuli-Responsive Nanoparticles

The core carriers of stimuli-responsive nanoparticles include liposomes, inorganic nanoparticles, hybrid materials, etc. It can flexibly trigger drug release, target activation, or imaging signal switching and other functions according to changes in external stimulation signals or disease microenvironments. For example, it can adjust the overall swelling rate of particles according to different pH values, enzyme activities, and temperature changes, which greatly improves the effectiveness and pertinence of drug treatment [21].

2.3 Preparation Technologies of Polysaccharide-Nano Delivery Systems

2.3.1 Electrostatic Self-Assembly

The electrostatic self-assembly technology forms a stable structure by the electrostatic interaction between positively charged polysaccharides (such as chitosan) and negatively charged nanoparticles (such as DNA, liposomes). Taking the preparation of β -glucan-chitosan nanoparticles as an example,

first, dissolve chitosan in an acidic sodium acetate buffer solution; then, drop the deionized water solution of glucan nanoparticles into the prepared chitosan buffer solution and carry out magnetic stirring to make the two fully contact and react; finally, remove the unbound components by centrifugal purification and obtain a pure and good-performance β -glucan-chitosan nano-delivery system through freeze-drying, providing strong support for the efficient delivery of drugs [22].

2.3.2 Covalent Coupling

The covalent coupling technology uses the active groups of polysaccharides to react with the surface groups of nanoparticles, thereby tightly combining polysaccharides and nanoparticles. Taking previous studies as an example, first, activate hyaluronic acid to obtain thiolated hyaluronic acid, and artificially introduce cysteamine groups to make it more reactive; then, modify paclitaxel nanoparticles to expose amino acid residues, creating conditions for subsequent coupling reactions; finally, covalently graft the carboxyl group of hyaluronic acid to the primary amino group in the amino acid residues of paclitaxel to form a stable hyaluronic acid-paclitaxel nanoparticle composite structure, significantly improving its delivery capacity for anticancer drugs [23].

2.3.3 Nano-Precipitation Method

The nano-precipitation method uses the incompatibility between organic solvents and aqueous phases to prepare polysaccharide-nano delivery systems. Dissolve polysaccharides and nano-carrier materials in organic solvents, then quickly drop them into an aqueous phase containing a stabilizer, and make the materials precipitate and form nanoparticles through solvent diffusion. When Zhang et al. prepared *Sargassum pallidum* polysaccharide nanoparticles, they used deionized water and absolute ethanol as solvents and antisolvents. After the two phases were fully mixed, the antisolvent was volatilized, and then concentrated and freeze-dried to obtain pure *Sargassum pallidum* polysaccharide nanoparticles [24]. This method is relatively simple to operate and can better control the size and morphology of nanoparticles.

3. Functions and Advantages

3.1 Enhanced Stability

3.1.1 Enhanced Physical Stability

In the biological application of nanoparticles, stability is a crucial performance index. Polysaccharides can significantly enhance the stability of nanoparticles and complement their competitive shortcomings. From the perspective of physical stability, the long-chain structure of polysaccharides can form a hydration layer barrier on the surface of nanoparticles, and efficiently reduce the collision and aggregation between particles through steric hindrance. Take chitosan-coated poly lactic-co-glycolic acid nanoparticles as an example. The coated nanoparticles have a 19% increase in size, a 16.73% increase in embedding efficiency, and a 27.06% increase in drug loading compared with the uncoated ones [25].

3.1.2 Enhanced Chemical Stability

In terms of chemical stability, the hydroxyl/sulfate groups of polysaccharides have the ability to quench reactive oxygen species, protecting the core of nanoparticles from oxidative degradation. For example, when hyaluronic acid-modified *Ligusticum chuanxiong* oil liposomes are used to treat human skin photoaging, the content of malondialdehyde (a marker of oxidative stress) can be reduced by 37.77 $\mu\text{mol/mg}$ [26].

3.2 Targeted Delivery

3.2.1 Passive Targeting

By modifying nanoparticles with polysaccharides, their particle size can be regulated to be between 50-200 nm, enabling them to enrich in lesions through the gaps (about 400 nm) of tumor

blood vessels. This passive targeting mechanism effectively avoids the accidental recognition of nanoparticles by the mononuclear phagocyte system, improves their stability in biological fluids, and enables drugs to reach the target area more effectively [27].

3.2.2 Active Targeting

Many polysaccharides have natural targeting receptors, which can deliver nanoparticles to specific target positions. For example, hyaluronic acid-modified nanoparticles have a strong tendency for solid tumors and can specifically interact with the overexpressed CD44 receptor in breast cancer cells, so that the tumor uptake rate is significantly higher than that of single targeting [28]. This active targeting strategy improves the targeting and therapeutic effect of drugs by specifically binding to receptors on the surface of tumor cells.

3.2.3 Microenvironment-Responsive Targeting

Wang et al. designed raspberry-like nanoparticles that change in size from 104 nm to 5 nm in the acidic tumor microenvironment. Such a sharp size change can promote local drug accumulation and effective penetration of drugs in tumors [29]. This microenvironment-responsive mechanism makes drug release more precise and reduces the toxic side effects on normal tissues.

3.3 Stimuli-Responsive Release

3.3.1 pH Response

The charge or conformation of polysaccharides will change with pH. For example, chitosan is protonated and dissolved in an acidic environment. Previous studies have shown that pH-sensitive chitosan-deoxycholic acid/alginate nanoparticles used for oral insulin delivery can protect the encapsulated insulin from degradation by gastric acid enzymes, and the oral bioavailability is increased by 15% [30].

3.3.2 Enzyme Response

The composite system can be degraded by specific enzymes. For example, nanoparticles prepared from sulfate- β -cyclodextrin and protamine have a better decomposition reaction to trypsin than other enzymes, so that the model substrate is encapsulated in the nanoparticles with high stability and released when treated with trypsin [31].

3.3.3 Redox Response

Polysaccharides containing disulfide bonds (such as thiolated chitosan) are rapidly broken due to the thiol-disulfide exchange reaction in the cytoplasm in the high-concentration glutathione environment of tumors, triggering release. This mechanism uses the redox characteristics of the tumor microenvironment to achieve precise drug release [32].

4. Application Fields

4.1 Food Field

4.1.1 Delivery and Controlled Release of Functional Food Ingredients

In the food field, nanoparticles are often used for the delivery and controlled release of functional food ingredients, such as vitamins and minerals. For example, chitosan-alginate nanoparticles can encapsulate nutrients containing vitamin C or iron ions and release them at intestinal pH to avoid destruction by gastric acid [33]. In addition, pectin-chitosan nanoparticles encapsulate probiotics, form a gel protection when passing through the gastric acid environment (pH 2-3), and release live bacteria after reaching the intestine when pectin is degraded by colonic enzymes, reducing the decrease in probiotic viability [34].

4.1.2 Food Preservation and Antibacterial Packaging

Nanoparticles also play an important role in food preservation and antibacterial packaging. Chitosan-silver nanoparticle composite films, due to their natural antibacterial properties combined with the slow-release bactericidal effect of silver nanoparticles, are used for coating and preserving fruits (such as strawberries), inhibiting the growth of molds, *E. coli*, and bacilli [35]. The nano-chitosan coating loaded with essential oils can significantly reduce the number of surface microorganisms on rainbow trout during storage at 4°C, extending the shelf life [36].

4.1.3 Intelligent Food Labels and Safety Monitoring

Intelligent food labels and safety monitoring are another important application of nanotechnology in the food field. The hybrid bacterial cellulose nanocrystal composite film developed by Pongpat Sukhavattanukul shows a visible color change by monitoring the hydrogen sulfide gas released during meat spoilage, intuitively displaying the freshness [37]. The gold nanoparticle-dextran sensor through ultra-stable aptamer conjugation can be used for the rapid detection of *Candida albicans* in food, preventing food residues caused by the tolerance of its spores to pasteurization [38].

4.2 Medical Field

4.2.1 Antitumor Drug Delivery

The application of nanotechnology in the medical field is expanding, especially showing great potential in antitumor drug delivery. Doxorubicin, as a widely used antitumor antibiotic, has significant curative effects, but its cardiotoxicity limits its clinical application. Studies have shown that forming nanoparticles by combining doxorubicin with hyaluronic acid can not only effectively reduce its cardiotoxicity but also improve the curative effect of the drug [39].

4.2.2 Vaccine Delivery

In terms of vaccine delivery, nanoparticle technology provides a new direction for vaccine development by enhancing immunogenicity and reducing dependence on adjuvants. For example, the glyco-nanovaccine based on oxidized acetal dextran nanoparticles has successfully induced a strong anti-SARS-CoV-2 response in mice [40]. These research results show that nanotechnology plays an important role in improving the safety and effectiveness of vaccines.

4.2.3 Anti-Infective Therapy

In the field of anti-infective therapy, carrageenan is a polysaccharide with antiviral activity extracted from seaweed. At present, studies have combined carrageenan with gold nanoparticles to form a composite, which can enhance the adsorption and inhibition of viruses and show potential in the prevention and treatment of coronaviruses [41].

4.3 Agricultural Field

4.3.1 Carriers for Pesticides and Fertilizers

The nanoparticle-polysaccharide composite system can be used as a pesticide carrier to achieve the slow and controlled release of pesticides by encapsulating pesticide molecules. For example, chitosan nanoparticles encapsulated with the herbicide paraquat can change its release rate, reduce environmental pollution, and improve the weeding effect [42].

4.3.2 Soil Improvement

In terms of soil improvement, nanoparticle-polysaccharide composite materials can adsorb the nutrients required in the soil and provide a continuous nutrient supply for plants with the help of a controlled release mechanism [43]. Some nanocomposites can also adsorb heavy metals in the soil, reducing their toxicity to plants. For example, the nanocomposite prepared from chitosan and montmorillonite can adsorb and remove herbicides in the soil [44].

4.3.3 Pesticide Residue Detection

In the field of pesticide residue detection, polysaccharide-based nanocomposites can be used to detect pesticide residues in soil and water. For example, the chitosan/gold nanosheet composite carrying plant esterase can be used for the ultrasensitive detection of organophosphate pesticides [45].

5. Challenges and Future Directions

5.1 Key Challenges

Process complexity is a major challenge. Natural polysaccharides have large molecular weights and wide spans, and their glycosyl compositions are complex, making the analysis of their physicochemical structures extremely difficult. The physicochemical structure of polysaccharides determines their physiological activities. Taking β -glucan as an example, its solubility and conformational changes will affect the affinity with target cell receptors.

In vivo characterization technologies also have bottlenecks. Although commonly used probe modification methods can track the distribution, absorption, and metabolism of particles in vivo, they cannot directly confirm the in vivo stability and tissue distribution characteristics of polysaccharide-nanoparticles.

5.2 Future Trends

Artificial intelligence (AI)-assisted design has broad application prospects in the future. AI technology can be used for the molecular design of composite systems. By simulating and predicting the physicochemical properties, drug loading capacity, and biocompatibility of polysaccharides, more precise material design can be achieved. At the same time, AI can analyze the individual characteristics of patients and design nanoparticle-polysaccharide composite systems for specific diseases and patients to improve the pertinence of treatment.

Bioinspired nanosystems are also a future development direction. In the future, more nanoparticle-polysaccharide composite systems based on cell membrane coating can be developed to make them have better biocompatibility and immune escape ability, and more effectively circulate in the body and reach the target tissue. The natural delivery mechanism in the body, such as the formation and function of extracellular vesicles, can also be imitated to develop nanoparticle-polysaccharide composite systems with similar characteristics for drug delivery.

However, this paper still has many shortcomings. First, the functional details are not sufficiently explored. Due to the need to cover a variety of materials, the description of each material may only stay at a superficial level, and the functional details are not deeply explored; second, the update has lag. Although the review has a certain timeliness advantage, the entire process from research, writing to publication may lead to some latest composite system construction strategies that cannot be reflected in the article in time; finally, the mechanism exploration is not in-depth enough. Limited by the length, the application mechanisms of many delivery systems have not been deeply expounded, and more in-depth exploration and research are still needed in the future.

In summary, this paper is the first to comprehensively and deeply summarize and analyze the types of polysaccharides and nanoparticles involved in the construction of delivery systems, and elaborate on the methods of constructing composite systems. It not only carefully explains the functions and advantages of the composite system but also summarizes its application effects in multiple fields, providing valuable references for the future application of polysaccharide-nanoparticle composite delivery systems.

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