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Research advances in chitosan-based polymeric materials: From intelligent carriers to targeted delivery

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ABSTRACT: In recent years, with the advancement of precision nutrition and biotherapy concepts, the demand for efficient and targeted delivery of functional active substances, especially probiotics, has become increasingly urgent. Chitosan, a natural, non-toxic, and biodegradable alkaline cationic polysaccharide, has emerged as a key material for constructing intelligent delivery systems due to its unique biological properties and modifiability. Chitosan-based delivery systems could not only passively protect their payload but also respond to specific signals in the gastrointestinal microenvironment, such as pH, enzymes, and redox potential, which enabled precise localization and controlled release of active ingredients like probiotics. This article aims to systematically review the latest research progress on chitosan-based polymeric materials as intelligent delivery carriers, focusing on their application in oral delivery. It analyzes their molecular design strategies, targeting mechanisms, construction methods, and efficacy evaluation, and discusses future development trends.

Keywords: Chitosan; Intelligent response; Targeted delivery; Oral functional factors

1. Introduction

The safe delivery of functional active substances to the site-specific location in the human body, with the effective enrichment as well as controlled release, had become a fundamental scientific challenge in the rapid development period in food science, biomedicine, and materials science[1]. he oral delivery efficiency of these active substances, which were key functional components for regulating intestinal microecology and maintaining host health, directly determined their bioavailability *in vivo* and the ultimate efficacy[2] [3]. Nevertheless, these substances needed to penetrate various competitive systems in the competitive world sequentially in every place before reaching the intestine and exerting their actions, including surviving in the gastric absorbed environment, digestive enzymes resistance and intestinal mucus barrier, and, finally, reaching a residence and functional expression in the competitive intestinal microenvironment [4] [5]. These multiple physiological barriers caused a significant portion of free active ingredients to be inactivated or lost before reaching the target site, severely limiting their practical application potential and efficacy[6].

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To confront these challenges, there was an urgent need to develop innovative delivery systems that could react intelligently to the gastrointestinal surrounding, as well as those that could proactively help the substances overcome these hurdles [7] [8]. In the context of functional foods and dietary supplements, this need is particularly acute. Bioactive ingredients such as probiotics, polyphenols, bioactive peptides, and vitamins often suffer from low oral bioavailability due to gastric degradation, poor intestinal absorption, or inadequate colonization. Chitosan-based carriers offer a practical solution by not only protecting these sensitive nutrients but also enabling their site-specific release in the intestine, thereby directly improving the efficacy of functional food products. Furthermore, the ability of chitosan carriers to modulate gut microbiota — for instance, by selectively delivering prebiotics or probiotics to the colon — opens new avenues for dietary interventions targeting metabolic syndrome, inflammatory bowel conditions, and immune regulation. Out of the numerous candidate materials, chitosan was distinguished because it had a distinctive integration of the properties [9]. Being one of the very few natural cationic polysaccharides known to exist in nature, chitosan had not only a good biocompatibility biodegradability, and low immunogenicity, but also rich amino groups in its molecular chains, which gave the material a range of designable intellible characteristics[10]. These amino groups enabled chitosan and its derivatives to respond to physiological signals in the gastrointestinal tract, such as pH gradients, specific enzymes, or redox potential, undergoing dissolution, gelation, or structural rearrangement to precisely release encapsulated active substances at the required time and location[11]. More to the point, the negative charge of the intestinal mucus layer and the cell membranes of bacteria were electrostatically attracted to the positive charge of chitosan leading to the design of delivery carriers with mucoadhesive or actively targeting characteristics or selective antimicrobial effects[12]. From a gut microbiota perspective, chitosan itself is not an inert carrier. Its degradation products — chitosan oligosaccharides — have been shown to exert prebiotic-like effects, promoting the growth of beneficial genera such as Bifidobacterium and Lactobacillus while inhibiting pathogens. When used as a delivery vehicle for probiotics, chitosan can synergistically enhance intestinal colonization, modulate short-chain fatty acid production, and reduce inflammatory markers, thereby contributing directly to host metabolic and immune health. Therefore, chitosan had evolved from a traditional embedding material into a key cornerstone for constructing intelligent targeted delivery systems[13]. Through molecular modifications such as carboxymethylation, quaternization, and thiolation, or by physically combining it with materials like alginate, pectin, and hyaluronic acid, researchers were able to precisely tune the mechanical strength, response sensitivity, biological adhesion, and release kinetics of chitosan-based carriers, thereby achieving directed functional enhancement for different stages of the active substance delivery process[14] [15].

The paper will review the latest developments in the field of research in the chitosan-based polymer materials as intelligent carriers of delivery systematically. It will initially examine the essence of physicochemical characteristics and biological merits of chitosan as a delivery vehicle. The molecular design strategies used to attain efficient delivery such as chemical modification and construction of composite system will be analyzed in detail. Subsequently, the focus will shift to their application in the oral

delivery of active substances and the intelligent targeting mechanisms utilized, such as pH responsiveness, enzyme responsiveness, and mucosal adhesion. At the same time, standard carrier building strategies, such as ionotropic gelation and layer-by-layer self-assembly, will be introduced in an overview and their protecting influence on the active substances and the effectiveness of the delivery will be outlined. Lastly, development trends in the field will be presented based on the existing issues in the field with the view to take theoretical reference and technical lessons on the design of next generation high-performance active substance delivery system.

2. Core characteristics of chitosan as an intelligent delivery substrate

2.1 Structural basis: Cationic properties and molecular modifiability

Chitosan had its characteristic molecular structure, and the peculiarities of its behavior were based on it. It was based on chitin, a natural polymer providing abundancy on crustacean exoskeleton, insect cuticles, and fungal cell walls. Chitosan was made through the N-deacetylation chemical reaction. It has a D-glucosamine and minor quantity of N-acetyl-D-glucosamine units bonded via 1, 4-glycosytic bonds [16]. Such a structure made it the sole alkaline cationic polysaccharide present in nature. The degree of deacetylation (DD) and the molecular weight (M_W) jointly defined the physicochemical and biological behaviors of it using two structural parameters [10].

The essence of the cationic nature of chitosan was the high number of free amino groups ($-NH_2$) of the molecule chains. These amino groups might be protonated to an $-NH_3^+$ under acidic or neutral conditions, which gave the polymer chain a positive charge[17] [18]. Such ability became the source of its range of smart properties, such as the pH responsiveness relying on the environmental change in the pH, the mucosal adhesion relying on electrostatic interaction with negatively charged biological surface, and the antimicrobial effects caused by its interaction with negatively charged bacterial cell membranes[19].

The chitosan chain was also dispersed with a lot of primary and secondary hydroxyl groups, together with amino groups. Two modifiable reactive sites of chitosan were formed by the combination of the amino and hydroxyl groups [20]. Certain functional requirements are specifically integrated into its molecular backbone through the use of chemical modification methods like carboxymethylation, quaternization, and thiolation, enabling directional regulation of material properties as hydrophilicity, charge density, and reactivity or giving it new environmental response properties [21]. At the same time, these active sites allowed chitosan to interact physically with other polymeric materials, including alginate and gelatin by either hydrogen bonding, ionic bonds and so on, building functionally integrated hybrid systems [18] [22]. Therefore, this inherent cationic nature and rich molecular modifiability together constituted the fundamental structural basis that enabled chitosan to evolve from a natural material into a multifunctional intelligent delivery platform.

2.2 Film-forming and gelation capabilities

Chitosan was employed to fabricate thin films and induce gelation, attributed to the abundant amino and hydroxyl groups along its molecular chains [23]. These groups were capable of forming stable three-dimensional network structures or dense flexible films in aqueous phases due to a number of interactions which included, ionic cross-linking, hydrogen bonding as well as entrapment by physical means. This characteristic formed the basis of materials science to develop the chitosan processing into various forms of delivery systems where such products were used in the form of hydrogels, microspheres, nanoparticles, and composite coating products.

This ability was the direct defining of the main functions of the delivery system. To begin with, it offered a wide selection of carriers to entrap different active substances with varying properties. Secondly, the developed system of gel and film may act as a barrier, which is tangible and therefore, isolates oxygen, gastric acid and digestive enzymes and therefore, protects the core of the items. By regulating cross-linking density, its swelling and degradation kinetics could be precisely designed for controlled release [22]. More importantly, the environmental responsiveness of the gel network was key to achieving intelligent delivery, for example, chitosan-alginate gels could contract for protection in the stomach and swell for release in the intestine [24](Fig.1). Furthermore, this property facilitated the integration of other functional materials into the network, enabling the construction of multifunctional, integrated intelligent delivery systems[25].

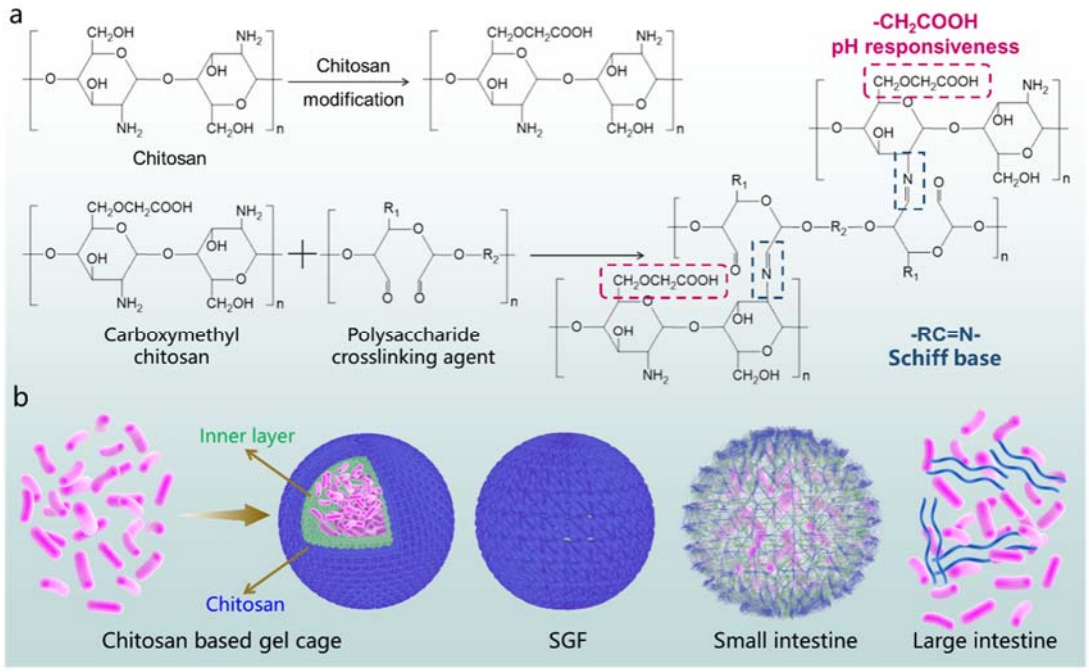


Fig.1 Carboxymethylation of chitosan and its application in probiotic delivery

2.3 Biosafety and Inherent bioactivity

The excellent biocompatibility, controllable degradability, and inherent bioactivity of chitosan collectively formed the safety cornerstone and functional advantages of chitosan as a delivery material, elevating it beyond the role of a mere physical carrier[10].

Biocompatibility and degradability were prerequisites for the clinical application of chitosan. Its good biocompatibility originated from its natural source and structure similar to glycosaminoglycans, resulting in

low irritation and weak immunogenicity to the organism. Simultaneously, chitosan could be gradually degraded by specific enzymes like lysozyme in physiological environments into non-toxic amino oligosaccharides or monosaccharides, which were ultimately completely absorbed or metabolized by the body, avoiding the long-term retention risks associated with non-biodegradable materials [26] [27]. These two attributes in delivery systems provided the high inherent safety of the carrier vessel per se, sufficiently compliant to the basic product needs of materials in food and pharmaceutical industries and offered a dependable delivery vehicle or green tunnel of active substance, *in vivo*, into the body. Chitosan was a therapeutically useful bioactive substance.

Particularly since it is inherently bioactive. Its main tasks consisted of: (1) Broad-spectrum antimicrobial effect: accomplished through the positively charged molecular chains to bind with negatively charged cell wall in bacteria, disrupting membrane integrity and inhibiting various pathogenic bacteria [28]. (2) Immunomodulatory and anti-inflammatory properties: it may control macrophage and anti-overexpression of pro-inflammatory functions of immune cells [29]. (3) Pro-healing effects: it may promote the growth of the fibroblasts and collagen and deposition[30].These natural activities might give rise to substantial synergistic activity with the loaded active substances during the delivery process. Indicatively, in case of probiotics administration, the antimicrobial property of the chitosan could be used to suppress intestinal pathogens and clear the microenvironment of new probiotic colonies [24]. Its immunomodulatory would be cooperative with the probiotics on the intestinal immune system and bidirectionally regulate the relationships between the carrier-microbiota, thereby forming synbiotic delivery systems with improved therapeutic functionality [31]. There still occurred, however, a central contradiction and design question; namely, how to offer adequate protection and delivery of probiotics which were themselves microorganisms taking the form of this widely antimicrobial chitosan? To overcome this paradox, scientists came up with brilliant space keeping plans. For instance, one research team constructed a double-layer hydrogel where the inner layer of carboxymethyl cellulose provided gentle protection for probiotics, and the outer layer of chitosan-based composite was responsible for gastric acid protection and intestinal adhesion[24] [33]. Chitosan primarily inhibits Gram-negative and Gram-positive pathogenic bacteria, while demonstrating low toxicity and high biocompatibility toward most probiotics (e.g., Lactobacillus, Bifidobacterium), thus exhibiting inherent strain selectivity. Its antibacterial activity occurs mainly in the intestinal lumen against pathogens, whereas probiotics are protected within the carrier microenvironment, enabling clear spatial and temporal separation. Antibacterial effects remove harmful microbes, and probiotics replenish beneficial flora; both actions synergistically improve intestinal microecology rather than antagonizing each other.

3. Molecular design strategies and modification methods for chitosan

To overcome the performance limitations of natural chitosan in certain delivery scenarios, such as poor solubility, insufficient pH response precision, difficulty traversing the gastrointestinal mucus layer, and weak intestinal adhesion, and to endow it with richer and more precise functions, researchers developed

systematic molecular design strategies[10]. These were primarily divided into two paths: chemical modification and physical composite/hybridization, aimed at achieving directed enhancement and intelligent upgrading of material properties (Fig.2).

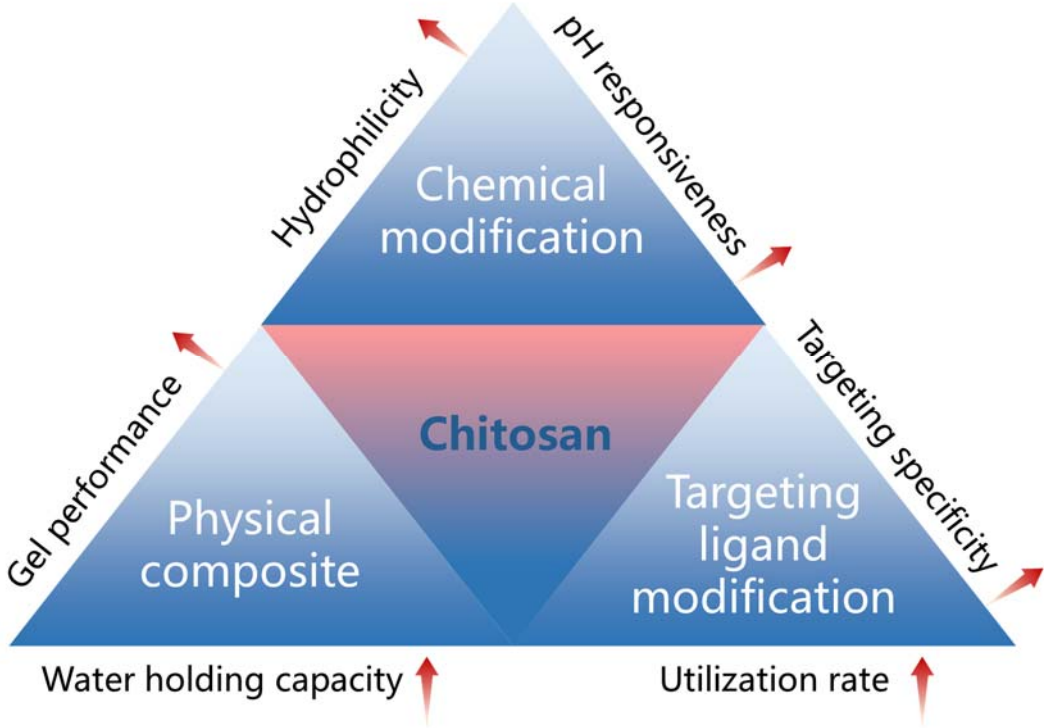


Fig.2 Molecular design and performance changes of chitosan

3.1 Chemical modification strategies

Chemical modification involved covalently introducing specific functional groups into the chitosan molecular skeleton, fundamentally altering its chemical structure to precisely and stably confer new materials with target properties. For example, carboxymethylation, by introducing carboxymethyl groups, significantly enhanced the hydrophilicity and pH responsiveness of chitosan [34]. Carboxymethyl chitosan-polydopamine hydrogels were shown to significantly improve the intestinal targeting and colonization of probiotics [22]. Quaternization introduced permanently positively charged quaternary ammonium groups onto the amino groups, allowing chitosan to maintain strong cationic characteristics even in neutral and alkaline environments, thereby substantially improving and stabilizing its antimicrobial activity and electrostatic interaction with mucosa [35]. Thiolation involved grafting thiol groups, enabling chitosan to form strong, durable disulfide bonds with cysteine residues in mucosal mucoproteins, achieving adhesion that far exceeded electrostatic adsorption and greatly prolonging carrier residence time in the gastrointestinal tract [36].

3.2 Physical composite/hybrid system construction

Physical composite and hybridization adopted another strategy: physically mixing or assembling chitosan with other functional materials through secondary bonds without altering its chemical structure, in order to build synergistic multifunctional systems. The most common strategy involved forming polyelectrolyte complexes or hydrogels with anionic polysaccharides like alginate and pectin via

electrostatic layer-by-layer self-assembly [22] [37]. This composite not only significantly improved the material's mechanical strength but also enabled more precise pH-responsive colon-targeted release by adjusting component ratios[24]. Furthermore, composite with polydopamine could introduce mussel-inspired super-strong wet adhesion [31]. These physical composite strategies were able to substitute the flaws of individual materials efficiently and offered flexible and varied solutions to satisfy the complex requirements of delivery[32].

3.3 Targeting ligand modification

The ligand modification approach of targeting was essential to attain the most sophisticated stage of accurate delivery down to a cellular level. In this approach conjugation of certain molecules was done on the carrier surface to make it actively recognize lesions. In tumor targeting, folic acid was commonly used to target overexpressed folate receptors, or RGD peptides targeted integrins on tumor vasculature[19]. For inflammatory diseases, mannose could be used to target activated macrophages [38]. In oral delivery, lectins or vitamin B12 could promote the specific absorption and transport of drugs across the intestinal epithelium [39]. In summary, chemical modification, physical composite/hybridization, and targeting ligand modification were three strategies that progressed layer by layer and complemented each other, collectively constituting the systematic toolbox for transforming chitosan into a high-performance intelligent delivery carrier.

4. Targeted delivery mechanisms of chitosan-based carriers

4.1 pH-responsive delivery

The pH-responsive delivery of chitosan-based carriers was their core and most classic intelligent mechanism for achieving oral targeting[31]. This mechanism directly utilized the natural pH gradient of the gastrointestinal tract from the stomach (pH 1.0~3.0) to the small intestine (pH 6.5~7.5) and then to the colon (pH 7.0~7.5). Its responsiveness originated from the protonation state change of the amino groups (pKa ≈ 6.5) on the molecular chains: in the acidic gastric fluid, protonated amino groups carried a positive charge, stabilizing the carrier structure and protecting acid-sensitive substances through the stomach. When exposed to neutral/alkaline intestinal conditions, the amino groups were deprotonated resulting in significant reduction of the chitosan solubility, and carrier disintegration by dissolution, swelling or ion exchange leading to a controlled discharge in the intestine.

In order to maximize the process, different creative carrier design strategies that would allow controlling the structural stability and disintegration behavior during varying pH levels precisely were developed by the researchers[24] [33]. The latter could be, e.g., the ion cross-linking of sodium tripolyphosphate to prepare gel beads to protect probiotics[40]. The establishment in polyelectrolyte-alginate complex was regarded as the golden standard in colon-targeted delivery, which would be effective in withstanding gastric acid and react by releasing in the intestine [24]. More precise control of the response pH value and release kinetics was achieved by introducing dynamic covalent bonds such as acylhydrazone

bonds or utilizing derivatives such as carboxymethyl chitosan [41]. Examples of the research indicated that carboxymethyl chitosan-oxidized sodium algorithm carboxymethyl cellulose hydrogel could be used to target the delivery of *Lactobacillus plantarum* to the intestine, where its transport to the intestine and oral utilization rate were significantly enhanced [24].

The chitosan pH sensitive mechanism had the potential to convert the innate principle of chitosan, acid-soluble, alkali-insoluble into an intelligent switch that would react to environmental conditions programmatically to modify the material with the help of molecularitarian engineering. Current research frontiers were dedicated to improving response precision by developing derivatives with more precise pKa and achieving more complex targeting logic by constructing multiple-response systems like pH/enzyme dual response[42]. The success of this strategy fully demonstrated how to combine the biological characteristics of materials with the needs of precision medicine, providing powerful technical insights for oral delivery systems, especially for targeted therapy of inflammatory bowel disease and colon cancer.

4.2 Enzyme-responsive delivery

Enzyme-responsive delivery was a high-precision targeting strategy based on biological recognition. Unlike mechanisms relying on physicochemical environments, it utilized enzymes specifically overexpressed at lesion sites as biochemical triggers to achieve precise spatiotemporal control of drug release. In the field of oral delivery, the core application of this strategy was colon targeting, because the colon was enriched with a vast and unique microbial flora that produced enzymes such as azoreductase, glycosidase, and polysaccharidase, which were almost absent in the upper gastrointestinal tract [43]. It has done so by developing carrier materials that were degraded specifically by these enzymes, thus blocking drug degradation and release in the stomach and small intestine and then releasing it specifically in the colon, allowing the highest level of colon-specific release.

In order to fulfill this objective, designing of the chitosan-based carriers were largely based on the notion of incorporating enzyme sensitive links or the adoption of polysaccharides that were degraded by particular enzymes. The most popular one was to incorporate azo bonds into the carrier, which could be specially cleaved by azoreductase released by colonic anaerobic bacteria, which is a classic colon-targeted delivery design over decades[44]. Also, direct use of the enzymatic degradation properties of the chitosan itself or some other polysaccharides was a significant course of direction. As an example, the microgels based on the specified chitosan might be degraded by lysozyme expressed at the inflammation sites of the colon, which could consequently result in the release of inflammation-targeted drugs [45]. Adding pectin to chitosan, or amylose and so on, would be able to use pectinase, or amylase released by colonic flora and cause the carrier to disintegrate [46]. Examples of research suggested that a drug release was attained using chitosan-azo polymer composite microspheres containing the anti-inflammatory drug 5-ASA because azo bond cleavage occurred in simulated colonic environment but had minimal release in the upper gastrointestinal tract thus greatly increasing efficacy and reducing systemic side effects [47].

Though enzyme-responsive design had a tremendous potential, its ability to respond strongly depended on the composition and the metabolic activity of individual colonic microbiota and this implied that there was inherent challenge of variability. The latest advances in research were dedicated to the solution of this limitation in the form of several and various response combinations and directing more specific systems reacting to one, clear species of enzyme. As an illustration, the creation of pH and enzyme dual-response systems was supposed to guarantee that Vehicles should resist the attack of gastric acid after which they should be broken down by colonic enzymes, or the creation of response systems that are designed to act upon a particular enzyme such as lysozyme[48]. These initiatives were propelling the management of colonic pathologies, including inflammatory bowel illness and colon-cancer, to smarter and more personal progression.

4.3 Mucoadhesive delivery

The intelligent approach aimed at the chitosan-based carriers was a core and essential approach of mucoadhesive delivery. Its fundamental principle was to enhance greatly the oral bioavailability of drugs by affecting an increase of residence time of carriers on the mucosal surface of the gastrointestinal tract, thus providing a higher absorption window. This action was mainly based on the great attraction by the positive charge of the protonated amino groups on the chitosan molecular chains within the physiological acidity and the attraction force of the negative charges in the surface of mucin that is the main constituent in the gastrointestinal mucosal layer. This early electrostatic interaction was further reinforced by hydrogen bonding, hydrophobic interaction as well as physical interpenetration/entanglement of polymer chains with the mucus network, which produced a tough adhesive layer that was reinforced effectively against peristaltic clearance. As an example, when treating gastric ulcers, direct adhesiveness of chitosan was used to build the local drug delivery systems that could closely attach to the surfaces of ulcers [49]. These systems did not only extend the residence and action time of antacids or growth factors at the region of lesion, they also were able to provide a physical protective layer on their own, compartmentalizing the ulcer against further gastric acid and pepsin erosion. At the same time the natural antimicrobial and pro-healing effects of chitosan may have a synergistic effect, giving the triple action of protection, drug delivery, and treatment.

Additionally, the chitosan was habitually made use of as an excellent model in intestinal delivery because of the possibilities of its local delivery to the intestine or systemic absorption of active agents through its good biocompatibility. But, in natural chitosan, protonation of the amino groups of the chitosan itself was suppressed in passing through neutral to strong alkalinity conditions at the intestine, and positive charges as well as electrostatic adhesive force were greatly reduced. Simultaneously, the dense and rapidly renewed intestinal mucus layer also posed a challenge to its effective penetration and long-term retention. Molecular design enhanced the functionality of researchers [22]. Neutralized carboxyl group ions and protonated amino functional groups in acidic gastric conditions made carboxymethyl chitosan a zwitterionic derivative, which could penetrate the carrier into the mucus layer. In the neutral intestinal environment, its carboxyl groups became completely ionized, yet electrostatic adsorption may change once the ratio of

hydrophilicity/hydrophobicity and mucus permeability is regulated, more stable intestinal adhesion and actin-natal release could be obtained (Fig.3). Also, with addition of other adhesive polymers such as polyacrylic acid and thiolation modification of the adhesive polymers to generate disulfide bonds with cysteine-containing domains of mucoproteins, systems that are more adhesive, specific, and more acceptable to oral delivery of macromolecules such as proteins and peptides could be prepared[50].

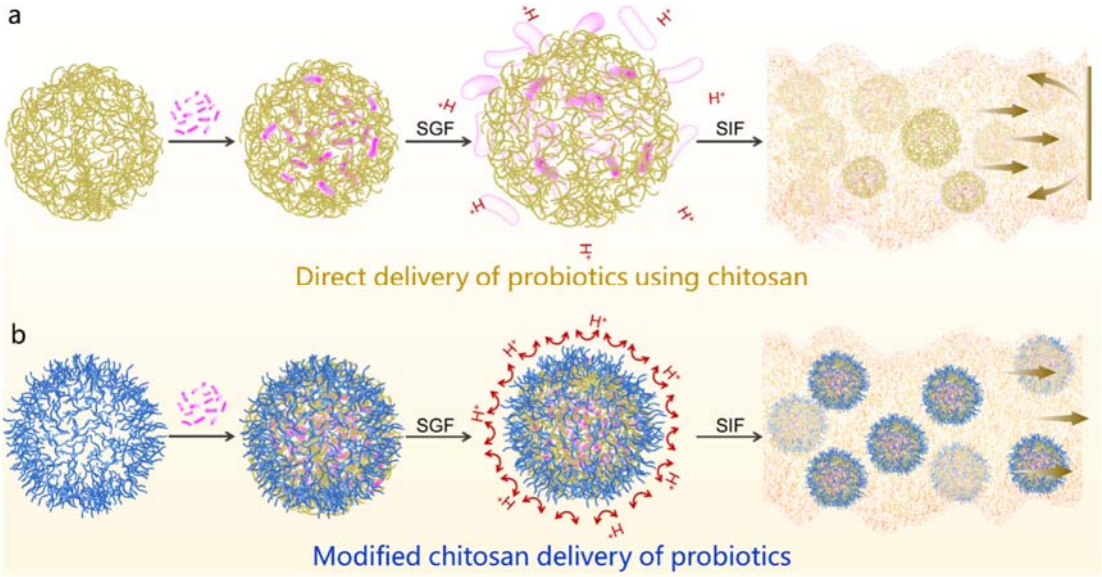


Fig.3 Carboxymethyl chitosan oxidized alginate polydopamine hydrogel can target probiotics for intestinal transport

Unlike native chitosan, whose adhesive capacity sharply declines in the neutral/alkaline intestinal environment due to deprotonation of amino groups (pKa ≈ 6.5), carboxymethyl chitosan (CMCS) achieves stable mucoadhesion through a multi-mechanism synergy rather than relying solely on carboxyl group ionization[51]. First, the ionized carboxyl groups (-COO^-) at neutral pH provide negative charges that electrostatically interact with positively charged domains of mucins. Second, the retained hydroxyl and amino groups on CMCS chains form extensive hydrogen bonds with mucin glycoproteins. Third, carboxymethylation significantly reduces chitosan crystallinity (from approximately 48% to 13%), conferring higher chain flexibility that facilitates physical entanglement with the mucus network. Fourth, the amphiphilic nature of CMCS — arising from introduced carboxymethyl groups and retained acetamido groups — enables hydrophobic interactions with mucin domains. This fourfold synergy (electrostatic, hydrogen bonding, chain entanglement, and hydrophobic effects) ensures stable mucoadhesion even under neutral/alkaline intestinal conditions, where native chitosan loses its adhesive capacity [52].

4.4 Emerging response strategies: composite response

In addition to the more novel response mechanisms that included the roles of pH and enzyme response, newer response mechanisms that address niche disease microenvironments were also becoming the focus of research. Microbial reaction went beyond recognition of an individual enzyme to reaction to the general reductive ambiance formed by colonic flora. An illustration is the creation of carriers with azo-aromatic bond or glycosidic bond which might be synergistically degraded by the hundreds of reductases or

glycosidases generated in microbial metabolism operations, resulting in more universal and stable colonic liberation than individual enzyme stimulators [53]. Redox response was mostly applied to the variation in intracellular reducing environments, particularly tumor cells and inflammatory locations [54](Fig.4). To reduce anomalies observed in using chitosan carrier intended for applications in blood circulation, the carrier was cross-linked with reduction sensitive bonds such as disulfide bonds attached to the carrier backbone that makes the carrier stable in the blood circulation under oxidative environment. The disulfide bonds were cleared effectively under high levels of glutathione once incorporated in tumor cells or macrophages, and could achieve intracellular-specific burst release of drugs, which enhanced the effectiveness of therapeutic efficacies and minimized systemic-toxicity [36].

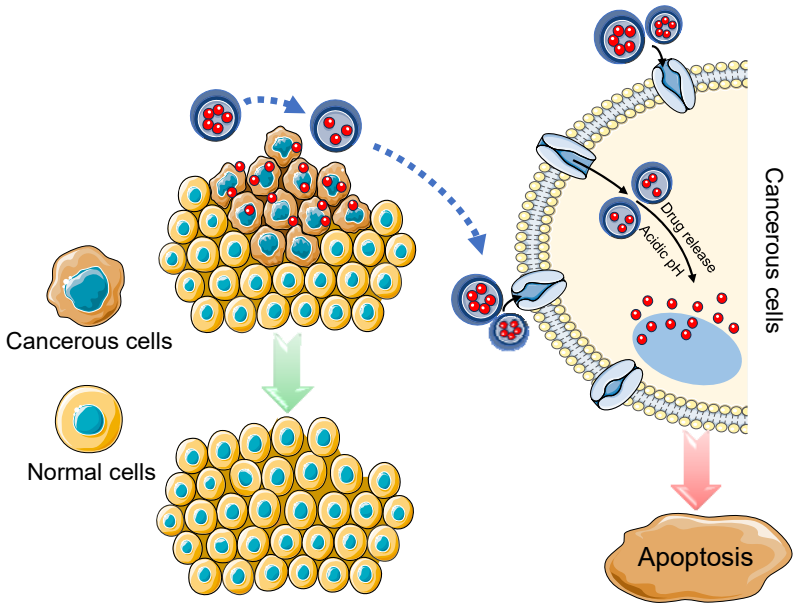


Fig.4 Chitosan carrier released anticancer drugs on cancerous cells in response to pH

Their combination and integration were the strength of these emerging strategies as they allowed building of smart systems with smarter response logic and more detailed targeting hierarchies. To construct a pH-enzyme-reduction triple-responsive carrier a cutting-edge design was to be undertaken. To begin with, the dependency on pH response as a protective mechanism of the drug via the stomach, when the carrier structure reaches colon, it started to disperse under the influence of the microbial enzymes. Finally, the high reductive environment achieved the ultimate release of the drugs after endocytosis by the target cells. This cascade response system was found to gain a jump of organ targeting to organelle targeting. Moreover, a combination of microbial response and external stimuli such as near-infrared photothermal therapy may help to give spatiotemporally controllable on-demand drug delivery. These extremely integrated intelligent designs embodied the development of chitosan-based delivery system of simple stimulus-response to the complex stage which would mimic a biological logic of environmental perception, judgment and action. They created an unprecedented technical opportunity of high precision of intervention in complicated diseases such as tumors and inflammatory bowel disease.

In food applications, pH-responsive and mucoadhesive delivery using simple chitosan complexes are preferred for their safety, low cost, and scalability. In pharmaceuticals, enzyme-responsive, redox, and

multi-stimuli systems are chosen for high precision. However, pH-response suffers from fixed pKa and incomplete release; enzyme-response is limited by individual microbial variation; mucoadhesion is weakened in the intestine; and complex responsive systems face high cost and poor scalability. Rational selection according to scenario and improvement of response accuracy and stability are key to future applications.

5. Carrier construction methods and their efficacy

The final success of acquiring the chitosan-based intelligent delivery systems was pegged directly on the accurate carrier formation procedures. Ionotropic gelation was a gentler method of physical encapsulation that optimally preserved the activity of substances such as proteins and probiotics but in many cases had to be used together with methods, including layer-by-layer (LbL) self-assembly. LbL actually facilitated nanoscale control of shell thickness and composition by electrostatic alternating deposition and served as an ideal substrate to fabricate multiple response intelligent carriers. In high production volumes emulsion-crosslinking and spray drying provided viable routes. The integration of these technologies is advancing the frontiers of the field. To illustrate this, ion-gelled core–shell hybrids, fabricated *via* LbL self-assembly, functioned as intelligent carriers. They exhibited high encapsulation efficiency, controlled release, and superior stability, thereby providing the physical foundation required to withstand complex *in vivo* conditions [55] [56].

Based on these ingeniously constructed carriers, the system first demonstrated excellent protective capacity for easily degradable substances. For fragile peptides, nucleic acids, and probiotics on the oral route, chitosan carriers could effectively resist erosion by gastric acid and digestive enzymes[57]. Studies showed that after encapsulation in alginate-chitosan microcapsules, the gastric acid survival rate of probiotics could be increased by several orders of magnitude, while chitosan/nucleic acid nanocomplexes could effectively protect them from degradation, ensuring the intact delivery of active ingredients[24].

While achieving effective protection, the system could further actively enhance the absorption of substances. The cationic nature of chitosan could transiently and reversibly regulate tight junctions between intestinal epithelial cells, improving paracellular permeability, and significantly prolonging contact time *via* mucosal adhesion. For macromolecular drugs, carriers could also promote active endocytosis by cells. The synergistic effects of these mechanisms enabled many poorly absorbed drugs loaded in chitosan nanoparticles to achieve significant enhancement of oral bioavailability, by several-fold to tens of times, in animal models [31] [33].

The complete logic from method construction to efficacy realization was validated through applied case studies in multiple fields. In drug delivery, chitosan-based colon-targeted systems constructed using technologies like LbL self-assembly became advanced strategies for delivering 5-aminosalicylic acid to treat inflammatory bowel disease [58]. In the field of functional foods, vitamins, prebiotics, etc., encapsulated *via* corresponding technologies also showed significantly improved stability and bioavailability. These successful cases connected the complete chain from intelligent carrier design to final functional output, fully

demonstrating the great potential and practical value of chitosan-based materials as a high-performance delivery platform.

6. Summary and future development trends

Research on chitosan-based polymeric materials had achieved a leap from exploring basic properties to constructing intelligent systems. Researchers have managed to successfully systematically generate various intelligent carriers that could accurately respond based on gastrointestinal pH, enzyme, redox potential, and microbial environment through systematic chemical modification, physical composite/hybridization, and targeting modification. These delivery systems did not only ensure great protection to delicate active components such as probiotics and proteins but also greatly improve their bioavailability *via* several actions such as mucosal adhesion, penetration enhancement, and programmed drug delivery. They exhibit strong application potential in both functional foods and targeted drug delivery, and provided an excellent roadmap of research design to be followed by the development of the functional realization.

Nonetheless, this shift of the sphere into the laboratory, clinical, and other unrestricted markets was not without a set of fundamental issues, and the challenges were the problems that had to be solved by further research. In the case of scalable production, numerous advanced methods of laboratory preparation experienced the problem of complicated scale up procedures, excessive cost, and low perfomance of a batch-to-batch quality. In regard to accurate delivery in the presence of complex organisms, the actual destiny of carriers in complex organisms, the contact with intestinal microflora, and of enormous physiological diversity among individuals were all challenges to the principle of universality and certainty of responsive systems. Extensive cumulative safety demanded formal and stringent testing of the toxicity, immunogenicity and possible accumulation hazards of more complex carrier substances.

In order to overcome these obstacles, future evolution would be based on three significant trends: (1) development, in the higher-order intelligent systems with capabilities of environmental perception and logical judgments. Vision of treatment process and adaptive adjustment Achieving visual monitoring of the treatment process and adaptive adjustment promotion of theranostics. (3) Hybrid convergence that includes the production of new, so-called active-carriers with built-in functions such as immunomodulation and gene editing that may lead to even disruptive technologies such as edible, so-called smart biochips **错误!未找到引用源。**. "

To conclude, the development of chitosan-based materials was pioneering the drive of adopting a paradigm shift in oral delivery, replacing the incumbent approach of using chitosan as the medium of loading a therapeutic factor, to the emerging conceptualization of active intelligence. In the context of functional foods and dietary supplements, this shift means moving from simple protection of ingredients to targeted modulation of the gut microbiome and host physiology. Its future would be in the way it tackled the issues of translation by thinking about them as systems engineers and, through a strong disciplinary convergence, finally converted these brainy solutions into useful instruments that would produce a benefit to human health.

Conflicts of Interest

The authors declare no conflict of interest.

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