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Chitosan-based oral colon-specific delivery systems for polyphenols: recent advances and emerging trends

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Oral colon-targeted delivery systems (OCDSs) have attracted great attention in the delivery of active compounds targeted to the colon for the treatment of colon and non-colon diseases with the advantages of enhanced efficacy and reduced side effects. Chitosan, the second-most abundant biopolymer next to cellulose, has great biocompatibility, is non-toxic, is sensitive to colonic flora and shows strong adhesion to colonic mucus, making it an ideal biomaterial candidate for the construction of OCDSs. Being rich in functional groups, the chitosan structure is easily modified, both physically and chemically, for the fabrication of delivery systems with diverse geometries, including nanoparticles, microspheres/microparticles, and hydrogels, that are resistant to the harsh environment of the upper gastrointestinal tract (GIT). This review offers a detailed overview of the preparation of chitosan-based delivery systems as the basis for building OCDSs. A variety of natural polyphenols with potent biological activities are used to treat diseases of the colon, or to be metabolized as active ingredients by colonic microorganisms to intervene in remote organ diseases after absorption into the circulation. However, the poor solubility of polyphenols limits their application, and the acidic environment of the upper GIT and various enzymes in the small intestine disrupt their structure and activity. As a result, the development of OCDSs for polyphenols has become an emerging and popular area of current research in the past decade. Thus, the second objective of this review is to systematically summarize the most recent research findings in this area and shed light on the future development of chitosan-based OCDSs for nutritional and biomedical applications.

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1. Introduction

An oral colon-specific delivery system (OCDS) refers to a delivery system that can, after oral administration, prevent the premature release of encapsulants in the stomach and small intestine but achieve the onset of release upon entry into the colon.[1] Benefiting from its ability to target any biomolecules (drugs or nutrients) to the colon, the OCDS can increase its local concentration, thus reducing the dosage, limiting the systemic absorption, and alleviating potential side effects when treating colonic diseases, including inflammatory bowel disease (IBD) and colorectal cancer (CRC).[2,3] Also, the colon could serve as the absorbing organ, allowing the absorption of peptides and proteins to enter the circulation *via* an OCDS with a high bioactivity that would otherwise be adversely affected by the low pH and protease concentration in the upper gastrointestinal tract (GIT), thus preventing non-colonic diseases.[4] Li *et al.*[5] found that liver hydrolysate delivered *via* colon-targeted capsules had a significantly improved protective effect on CCl_4-induced liver damage in rats compared with liver hydrolysate administered intragastrically *via* gavage. For designing an OCDS, materials that are inexpensive, green, and, importantly, responsive to the specific factors in the colon, are preferred.

Chitosan, a polysaccharide with a linear structure composed of β-(1–4)-2-amino-D-Glc units and some β-(1–4)-*N*-acetyl-D-GlcN units, is naturally derived from the shells of crustaceans such as shrimp, lobsters, and crabs.[6] Apart from being cheap, widely available, biocompatible and a safe biomaterial,[7] chitosan has many functional properties that are suitable for the development of OCDSs. Firstly, chitosan is only metabolized by enzymes of the colonic microbiota, especially *N*-acetyl-β-D-glucosaminidase, which acts on the β-(1/4) linkage of chitosan, with the potential to release the entrapped drug in the colon.[8,9] Another outstanding feature of chitosan is its mucoadhesion, which is due to the strong electrostatic interactions between the positively charged amino groups of chitosan and the negative charges from sialic acid present on the mucus surface, as well as hydrogen bonds and hydrophobic interactions, with a wide range of applications as the carrier.[10–12] Besides, chitosan presents good film-forming properties, so it could be used as a coat to bring about the improved physicochemical stability and bioavailability of drugs, tissue–cell interactions, and controlled release to the carriers.[13] Importantly, being rich in functional groups, the chitosan structure is known for its ease of physical and chemical modifications for the fabrication of delivery systems with diverse geometries, including nanoparticles, microspheres/microparticles, and hydrogels, which could meet various production needs.

Polyphenols, *i.e.*, organic compounds characterized by multiple phenol units, are found ubiquitously in plants. Until now, more than 8000 types of polyphenol are known, which can be divided mainly into phenolic acids, flavonoids, stilbenes, and lignans, depending on the number of phenolic rings and the interconnection of those rings (Fig. 1).[14] A growing area of research interest in polyphenols is for their use in the management of colonic health, as novel interventions to alleviate the symptoms of colon diseases.[15,16] Besides, the axis established between the gut and other organs, including the liver, brain, lungs, and heart, pushes gut health to a vital position as the center of body health.[17] Thus, the protection provided by polyphenols could be extended to liver failure, cardiovascular disease, cognitive disorders, and so on *via* their interaction with colonic microbes[18–22] (Fig. 1). Unfortunately, the hydrocarbon structure of polyphenols leads to their poor aqueous solubility, while the presence of hydroxy moieties impairs their lipophilicity, leading to limited applications in the food and pharmaceutical fields.[23] Besides, as an active functional group, hydroxy is extremely susceptible to light, heat, and oxygen from the external environment, and it is also vulnerable to physiological factors like digestive enzymes and the pH conditions before reaching the colon.[24] Therefore, to improve the biological efficacy of polyphenols, suitable carriers for the encapsulation and specific delivery of polyphenols to the colon have been developed. This review offers a comprehensive description of different design principles of OCDSs based on the properties of the GIT, followed by a detailed overview of the preparation of chitosan-based delivery systems, including nanoparticles, microparticles/microspheres, and hydrogels. In addition, the delivery of polyphenols *via* the chitosan-based OCDS is systematically summarized to shed light on further developments for nutritional and biomedical applications.

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2. The rationale for designing an oral colon-specific delivery system

An illustration of the OCDS is displayed in Fig. 2a. Considering the distal location of the colon in the GIT, the OCDS needs to travel through the entire GIT, so a comprehensive understanding of GIT physiology is required for the design of such carriers that are capable of efficiently delivering drug molecules to the colon. Overall, the physiological differences of the GIT can be generally classified by several important properties, including the pH and

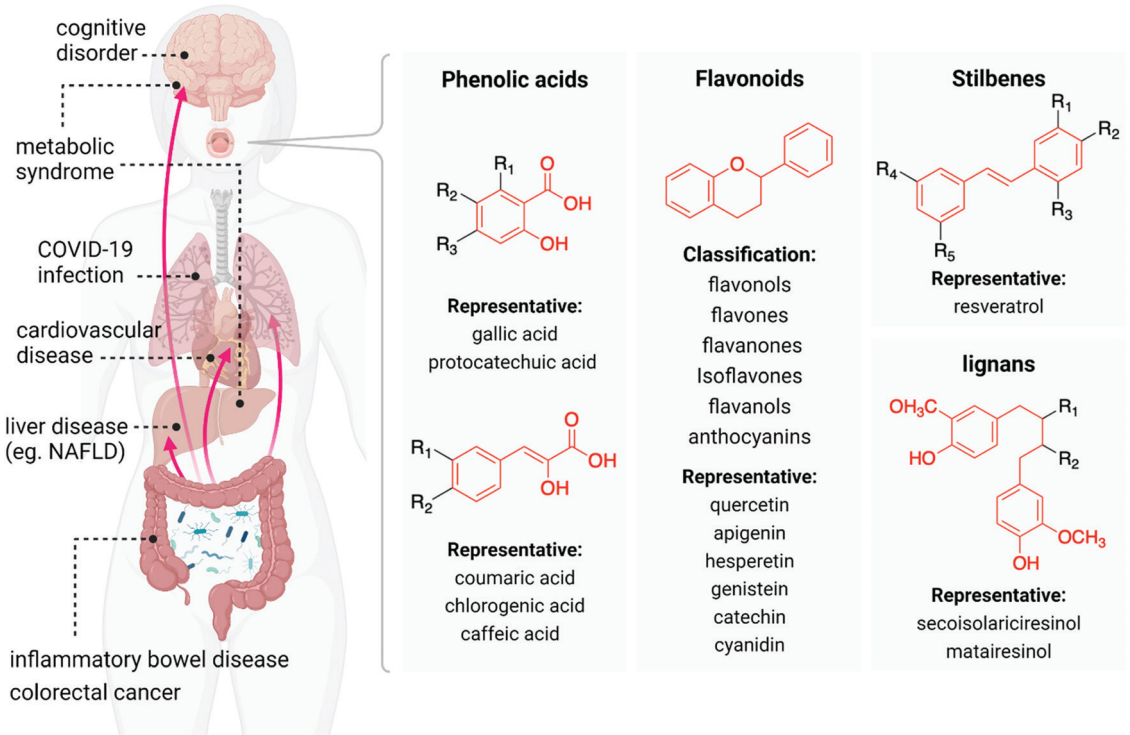

Fig. 1 Polyphenol classification and brief illustration of the polyphenol benefit on colon and non-colon organs *via* various gut–organ axes. The figure was created using BioRender (**https://biorender.com/**).

transit time, and the specific index in the colon, which includes the pressure and microbes/enzymes. Besides, the mucus in the colon has double-sided applications, and ligands or compounds responding to the colon disease improve the specificity[25,26] (Fig. 2b and c). To fully illustrate the design principles, some most commonly studied OCDSs prepared using polysaccharides, mainly but not limited to chitosan, are summarized and presented in Table 1.

2.1 pH-Dependent delivery

As shown in Fig. 2b, the pH value varies from one compartment to another along the GIT, with the oral cavity of pH 6.7–7.3,[51] the stomach of approximately pH 1.0–2.5, the small intestine ranging from pH 6.63 ± 0.53 in the jejunum to pH 7.49 ± 0.46 in the ileum, and the colon of pH 6.37 ± 0.58, 6.61 ± 0.83, and 7.04 ± 0.67 for the ascending, the transverse and the descending parts, respectively.[52] According to the different pH environments

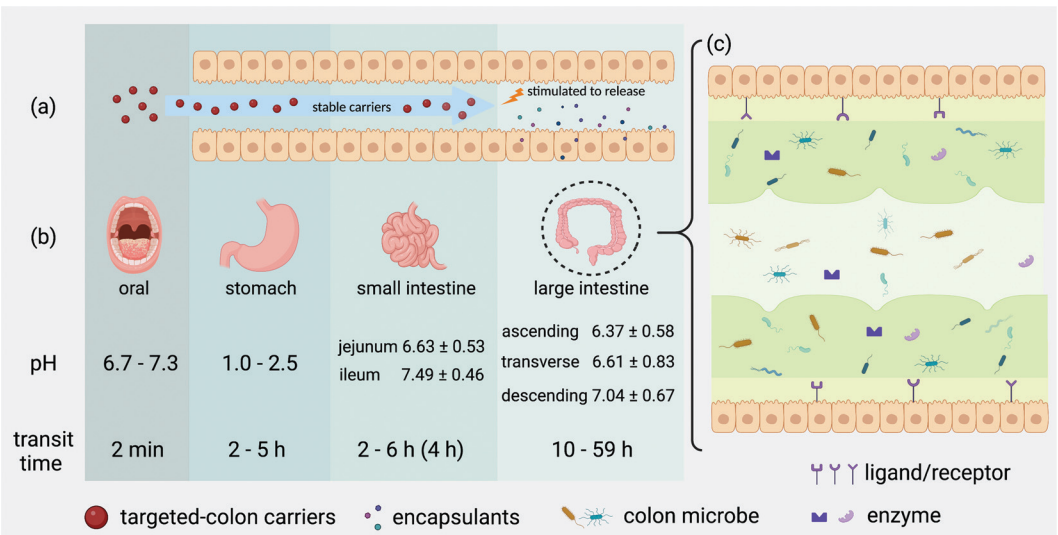

Fig. 2 Illustration of the oral colon-specific delivery system (a); gastrointestinal tract physiological factors that influence the colon-specific delivery system (b and c). The figure was created using BioRender (**https://biorender.com/**).

Table 1 Selected polysaccharide-based oral colon-specific delivery systems

Polysaccharide	Delivery system	Active compound	OCDS type	Ref.
Single				
Chitosan	Poly(vinyl alcohol)–chitosan/fumed silica nanocomposite hydrogel	Cisplatin	pH	27
Chitosan	Chitosan microparticles coated with Eudragit® S 100	5-Aminosalicylic acid	pH, and microbe/enzyme	28
Chitosan	Chitosan-pyromellitic dianhydride amic acid hydrogel	Ronidazole	Time, pH, and microbe/enzyme	29
Chitosan	Chitosan nanoparticles coated with Eudragit® S 100	5-Aminosalicylic acid	pH	30
Alginate	Alginate microspheres	Astaxanthin	pH, and Microbe/enzyme	31
Alginate	Chondroitin sulfate-alginate microspheres	5-Fluorouracil	pH, and microbe/enzyme	32
Pectin	Pectin-*graft*-polyacrylamide hydrogel	Budesonide	pH, and microbe/enzyme	33
Carboxymethyl cellulose	Carboxymethyl cellulose-*graft*-polyacrylamide/magnetic montmorillonite nanocomposite hydrogel	Diclofenac sodium	pH, and mucoadhesiveness	34
Guar gum	Guar gum oleate-*graft*-poly(methacrylic acid) hydrogel	Ibuprofen	pH, and microbe/enzyme	35
Guar gum	Guar gum succinate microparticles	Ibuprofen	pH, and microbe/enzyme	36
Gum karaya	Gum karaya-*graft*-polyacrylamide microspheres	Capecitabine	pH, and microbe/enzyme	37
Combined				
Chitosan/alginate	*N*-Succinyl-chitosan/alginate blend microspheres	Zinc and 5-aminosalicylic acid	pH	38
Chitosan/alginate	Aminated-chitosan/alginate microbeads	Bovine serum albumin protein	pH	39
Chitosan/alginate	Hydroxyethylacryl-chitosan/sodium alginate hydrogel	Paracetamol	pH	40
Chitosan/alginate	Chitosan/sodium alginate hydrogel	5-Aminosalicylic acid	pH	41
Chitosan/starch/pectin	Retrograded starch/pectin microparticles containing chitosan nanoparticles	5-Fluorouracil	Microbe/enzyme, mucoadhesiveness	42
Chitosan/pectin	Chitosan/pectin microbeads	Anti-A/B toxin immunoglobulin of egg yolk (IgY)	pH, and microbe/enzyme	43
Chitosan/hyaluronic acid/β-cyclodextrin	Chitosan/hyaluronic acid/hydroxypropyl-β-cyclodextrin nanoparticles coated with Eudragit® S 100	Tacrolimus	pH, and ligand/receptor	44
Alginate/hyaluronic acid	Alginate/thiolated-hyaluronic acid hydrogel microspheres	Thiolated-hyaluronic acid	Time, pH, mucoadhesiveness and ligand/receptor	45
Alginate/β-cyclodextrin	Alginate/tri-*O*-sulfonyl-β-cyclodextrin nanogel	5-Fluorouracil	Pressure	46
Alginate/guar gum	Sodium alginate/guar gum succinate beads	Ibuprofen	pH, and microbe/enzyme	47
Alginate/carboxymethyl cellulose	Calcium alginate/carboxymethyl cellulose beads	5-Fluorouracil	pH, microbe/enzyme, and mucoadhesiveness	48
Alginate/pectin	Alginate/pectin microspheres coated with Eudragit® S 100	Cisplatin	pH, and microbe/enzyme	49
Gellan gum/pectin	Gellan gum/pectin beads	Resveratrol	pH, microbe/enzyme, and mucoadhesiveness	50

in each part of GIT, a pH-dependent OCDS is designed in such a way that they only release the encapsulates in the colon.

Polymethacrylates, with the most commonly used commercial enteric coating polymers being Eudragit®, are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in different ratios. Eudragit® S 100 and Eudragit® FS 30D can maintain a compact structure at pH 1.2 but dissolve at pH 7.0, achieving the purpose of localized drug delivery in the colon.[53] Some studies[30,44] have reported Eudragit® S 100 chitosan-based nanoparticles for the delivery of drugs for IBD treatment. *In vitro* drug release showed that within the first 2 h, $<10\%$ of the drug tacrolimus was released in simulated gastric fluid (SGF) at pH 1.2; during the following 4 h, the accumulated release of the drug was 9.1% in simulated intestinal fluid (SIF) at pH 6.8, indicating that less drug was released from the nanoparticles in the upper GIT; over the remaining period of 18 h, the drug was sustainably released in simulated colonic fluid (SCF) (pH 7.4).[44] However, since synthetic polymer-containing materials may trigger adverse immune responses, natural polysaccharides, especially chitosan and alginate, have emerged as substitutes.[38–41]

With the advantages of readily available carrier materials and a simple preparation process, the pH-dependent approach has received extensive attention. However, it has also been confirmed that the pH can be affected appreciably by an individual's diet and physical condition, which can lead to premature or delayed disintegration of the carriers, thus affecting the effects of drug treatment. Gastric pH values in the fed state range from 2.7 to 6.4, and the pH in the upper small intestine tends to be lower in the fed compared with the fasted state.[54] The pH in the inflammatory colon is 2.3–5.5, even lower than that in the small intestine.[55] Even for a standard individual, there are similarities in pH between the small intestine and the colon, which limits the application of a simple pH-dependent OCDS. Interestingly, the pH-dependent OCDS could play a key role in improving the delivery efficiency and accuracy when combined with other kinds of OCDSs.

2.2 Time-dependent delivery

In time-dependent OCDSs, drug release from the system occurs after a pre-determined lag time that corresponds to the transit time from the mouth to the colon. The normal range of transit times includes the following: 2–5 h for the gut, 2–6 h for the small intestine, and 10–59 h for the colon.[56] The retention time is highly variable with dietary intake, physical state, age,

gender, *etc.* The gastric transit time is 0–2 h in the fasted state but extends to 0–6 h in the fed state, depending on the type of diet.[57] The physical state with gastroparesis and type-2 diabetes would see a prolonged gastric transit time.[58,59] Thus, the onset of the initial drug release might occur in the small intestine in some subjects, while in others, the formulations may pass the ascending colon intact, suggesting that single time-dependent systems are not ideal for delivering drugs to the colon. Fortunately, the running time in the small intestine is relatively constant,[60] with an average of 4 h, implying that the OCDS with a combination of pH-dependent and time-dependent properties can help to overcome premature drug release in the stomach and, in turn, stabilize the release efficiency of single factor-dependent drug-delivery systems.

In recent years, time-controlled pulsatile drug-delivery technology has attracted attention because these systems deliver the drug at the right time, at the right site of action, and in the right amount. One of the earliest time-dependent release formulations is the Pulsincap™ device, which consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug. When the capsule comes into contact with a dissolution fluid, the plug swells, and after a lag time, the plug pushes itself outside the capsule to rapidly release the drug.[61] Apart from the capsule-shaped system with a release-controlling plug, there have also been delivery systems that contain an erodible coating layer divided into the bulk-eroding system and surface-eroding system, and a delivery system with a rupturable coating layer, which has been described by Jain *et al.*[62] in detail. If acid resistance is imparted, these systems would only come into play in the small intestine, regardless of the gastric emptying, and the drug release can be achieved after entering the colon by adjusting the dosage and ratio of time-responsive materials. For example, Liu *et al.*[45] designed colon-targeted core–shell hydrogel microspheres with alginate as the shell. The alginate shell had resistance to acid, so the microspheres remained intact during the gut period and started to thin after entering the small intestine. By optimizing the timing of cross-linking reaction between alginate and Ca^{2+} to form a shell of 8 μm thickness, the requirement that the active core is protected in the small intestine for 4 h but is released in the colon was met.

The preparation of a time-dependent OCDS is more complicated, where advanced technology, trained personnel, and adequate finances are needed.[63] Another kind of undirected time-dependent OCDS could be established by combining a pH-dependent OCDS and a colon-specific-property-dependent OCDS, which include pressure and microbes. The acid-resistant property helps the carrier to pass through the gut, while pressure or microbial degradation enables the carrier to decompose in the colon to release the contained drugs, as discussed below.

2.3 Pressure controlled-dependent delivery

The colon is the main part of the large intestine in which water and electrolyte reabsorption occur. As water reabsorption leads to an increase in the consistency of the colonic contents, the intestinal wall exerts more pressure on the contents when the intestinal tract is peristaltic. This pressure enables the carrier to disintegrate and release the drug. Based on this mechanical principle, a pressure controlled-dependent OCDS has been designed.

Hosseinifar *et al.*[46] reported an easy process for the synthesis of pressure-sensitive nanogels that aim to deliver 5-fluorouracil. Briefly, alginate was cross-linked with β-cyclodextrin to produce hydrogels; then nanoparticles were obtained through an emulsification method; finally, 5-fluorouracil was loaded into the nanogels easily by mixing the two in an aqueous solution. The release experiment of 5-fluorouracil in response to pressure showed that the drug release from the nanogels could be increased by applying the pressure because it could change the inclusion ability of the β-cyclodextrin moieties. However, when a human experiences fasting, eating, and laxative conditions, the pressure in the colon varies greatly,[64] which uncontrollably affects the release kinetics of the drug molecules from a pressure-controlled-dependent OCDS.

2.4 Microbe/enzyme-dependent delivery

The human GIT harbors a complex and dynamic population of microorganisms. Due to the strongly acidic conditions in the stomach and the high levels of oxygen and anti-microbials in the small intestine, relatively few species of bacteria are generally present; by contrast, however, the conditions of the colon support a dense and diverse community of bacteria.[65,66] Statistically, the size of the bacterial load increases gradually from the stomach (10^1–10^3 CFU ml^{-1}) to the jejunum (10^4–10^7 CFU ml^{-1}) to feces (10^{11}–10^{12} CFU ml^{-1}), with the ascending diversity of microbiota.[67] About 10^{13}–10^{14} microorganisms have been classed into more than 500 different microbial flora types in the colon, and are dominated by the strictly anaerobic *Bacteroides*, *Eubacterium, Bifidobacterium*, *Fusobacterium*, *Peptostreptococcus*, and *Atopobium* genera.[68] These bacteria can produce a variety of enzymes, including azoreductase, β-glucuronidase, β-galactosidase, β-xylosidase, α-arabinosidase, nitroreductase, deaminase, and urea hydroxylase, for the metabolism of polysaccharides that are otherwise indigestible in the small intestine, and thus such polysaccharides could be applied to prepare a microbe/enzyme-dependent OCDS.[69]

Alginate microspheres were fabricated to deliver astaxanthin, an excellent antioxidant, to the colon, and *in vitro* models showed that the microspheres could tolerate well the conditions in the mouth, stomach and small intestine, and reach the colon where astaxanthin was released due to the fermentation of gut microbiota.[31] Although specifically degraded in the colon, many polysaccharides are hydrophilic and swell under exposure to the upper GIT, leading to premature drug release. Thus, researchers usually use a combination of polysaccharides to overcome this shortcoming. Seeli *et al.*[47] prepared sodium alginate/guar gum succinate beads cross-linked with barium ions to deliver ibuprofen. These beads had susceptibility to microbial degradation and controlled drug-release properties due to the presence of guar gum succinate, as well as a pH-sensitive character due to the presence of sodium alginate, resulting in the colon-targeted delivery. In addition, other strategies may also be applied for

the better design of microbe/enzyme-dependent OCDSs, including the use of enteric coatings[28,49] and chemical modification.[32–37]

2.5 Mucus

Mucus is a complex aqueous fluid that contains 90–95% water, 1–5% glycoprotein mucin, 1% electrolytes, 1–2% lipids, and other smaller proteins.[70] On the surface of the colon epithelial layer, there are two layers of mucus built from MUC2 protein, consisting of a loosely adherent outer layer for bacterial adhesion and a tightly adherent sterile inner layer. The constituent monomers of MUC2 with ~0.6-μm-long stiff rods are covalently interlinked as dimers in their C-terminus and as trimers in their N-terminus, thus forming large net-like structures with a <200 nm pore size.[71,72] As a result, the colonic mucus is 830 μm thick on average (715 μm for the outer layer, 115 μm for the inner layer) and had viscoelastic, lubricating, and hydration properties.[73] Since the mucus layer is present throughout the GIT, albeit with some structural differences,[74] this is not a suitable principle for the construction of OCDSs. However, mucus could interfere with the biological fate of the OCDS.

Leung and Robinson[75] described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesive carriers enable prolonged retention at the application site and provide a controlled rate of drug release to improve the therapeutic outcome,[76] and have thus received a great deal of attention over the past few decades, where polysaccharides have shown an excellent performance.[11,77,78] However, the colon does not appear to be an ideal place for mucoadhesive carriers to function, as the released drug may not reach the enterocytes in time due to the excessively thick mucus layer. Thus, mucopenetrating particles with a broader particle distribution and deeper penetration of the mucus gel layer have come into being for GIT delivery.[79,80] A comparison study conducted by Maisel *et al.*[81] found that mucoadhesive particles aggregated in mucus in the center of the GIT lumen, far away from the absorptive epithelium, both in healthy mice and in a mouse model of ulcerative colitis, while mucopenetrating nanoparticles deeply penetrated the mucus to reach the epithelial surface.

On the other hand, the presence of mucus in the colon has a beneficial side effect for drug function. Prodrugs are inactive pharmacological molecules that undergo a spontaneous or enzymatic reaction *in vivo* to release the active drug. The extended retention time in the mucus *via* mucoadhesive carriers promotes the adequate metabolism of encapsulants *via* microflora, to optimize the prodrug approach specifically targeted to the colon.[82] The most classic example is sulphasalazine, a prodrug that consists of the active ingredient 5-aminosalicylic acid for the treatment of IBD,[83] and the first relevant system was established as early as 1992.[84] Thus, the different effects of the mucus layer need to be considered when choosing the delivery system for active compounds.

2.6 Ligand/receptor

Ligand/receptor-mediated cellular events have received significant attention in drug delivery because they are the best tool for designing site-specific and target-oriented delivery systems, contributing to the increased therapeutic effects while reducing toxic side effects significantly.[85,86] A large body of literature is available on the treatment of colon diseases *via* ligand/receptor-mediated drug-delivery systems,[86–89] and this review details the involved ligands when discussing the chitosan-based OCDS for delivering polyphenols in the following section. Besides, there is no doubt that the combination of a ligand/receptor-mediated delivery system with pH-dependent systems maximizes its GIT stability and the release of the drug to the intestinal-colon track.[90]

3. Preparation of chitosan-based oral delivery systems

Being rich in functional groups, the chitosan structure is known its for easy physical and chemical modification for the fabrication of delivery systems with diverse geometries, meeting various requirements in the field of food and drugs. As for physical modification, blending or physically mixing two or more polymers may be the easiest and simplest way to create a new composite with various physical properties. As for chemical modification, the amino groups of chitosan can undergo several chemical reactions like alkylation, quaternization, grafting, and reaction with aldehydes and ketones. Besides, due to the abundance of hydroxyl groups, chitosan can also participate in many other reactions, such as H-bonding with polar atoms, *O*-acetylation, cross-linking and grafting.[91–93] This review mainly focuses on the preparation of three types of chitosan carrier: nanoparticles, microspheres and hydrogels (Fig. 3).

When it comes to preparation, the molecular weight and degree of deacetylation (DDA) of chitosan should be taken into

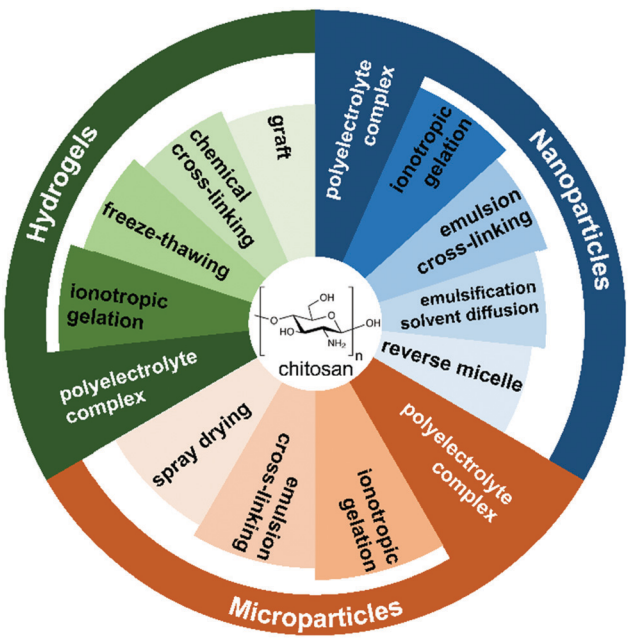

Fig. 3 Summary of methods for fabricating chitosan-based nanoparticles, microparticles/microspheres and hydrogels.

consideration. The size and surface charge are the two fundamental physicochemical properties closely related to the performance of carriers *in vitro* and *in vivo*,[94] which are therefore inevitably detected in characterization. Generally, the size of chitosan carriers is positively related to the molecular weight, while the surface charge is not obviously influenced.[95] On the other hand, the chitosan solubility depends directly on the DDA, because more amine groups with an increasing DDA could be protonated to be soluble.[96] Chitosan, with a DDA of 70–85%, might be partly dissolved in water, and with a DDA of 85–95% it has good solubility in water, although it is difficult to achieve a DDA of 95–100%.[97] Usually, in most biomedical experiments and applications, the DDA ranges from 75% to 90%,[98] whereas in China only a DDA of higher than 85% could be acceptable to the food industry (GB 29941-2013). Interestingly, it was reported that mucoadhesion, an important property for the function of the OCDS (discussed above), could be influenced by both the molecular weight and the DDA, where the higher the molecular weight, the lower the DDA, and the higher the mucoadhesion.[4]

3.1 Chitosan nanoparticles

Nanoparticles are a type of spherical structure with a nanoscale diameter between 1 and 100 nm,[99] although it sometimes may be up to 500–1000 nm.[100] Many methods have been reported for fabricating chitosan nanoparticles, such as ionotropic gelation,[101] the polyelectrolyte complex (PEC) method,[102] the emulsion cross-linking method,[103] emulsification solvent diffusion,[102] and reverse micellar methods.[104] The latter three methods need a bulk of organic solvents to produce nanoparticles, which may be toxic if they are not removed completely from the nanoparticle dispersion. Thus, ionotropic gelation and PEC are the most widely used methods of production, especially for oral-delivery applications. The common mechanism of these two methods for fabricating nanoparticles is that in an acidic environment, protonation of the chitosan amino groups makes it form a gel in the presence of specific polyanions *via* inter- and intra-molecular cross-linkages.[105] However, there are some differences between them according to the species of anion used.

Generally, ionotropic gelation employs electrostatic interactions between the negatively charged groups of small anionic molecules and the positively charged amine groups of chitosan.[106] Tripolyphosphate (TPP), which has been recognized by the US FDA (GRAS 582.6810) as a safe substance when used in accordance with good manufacturing or feeding practices, has long been used to form chitosan nanoparticles. In detail, this method involves the addition of TPP solution to a chitosan acidic solution under mild magnetic stirring for a specific time at room temperature.[107,108] Chitosan nanoparticles are formed spontaneously upon mixing, turning into a colloidal dispersion with a milky or opaque appearance depending on the concentration and ratio of chitosan and TPP.[109,110] Usually, the reaction is also strongly associated with pH to produce the appropriate positive and negative charges, where pH 5 is commonly selected.[111,112] Finally, the nanoparticles are isolated and collected *via* centrifugation, and then subject to freeze-drying to obtain a powder, which may be stored at 2–8 °C for further use.

PEC is also referred to as interfacial coacervation or complex coacervation, which commonly uses anionic macromolecules to produce chitosan nanoparticles. Anionic macromolecules can be any biopolymers with a negatively charged surface, either proteins, including casein[113] and zein,[114] or polysaccharides, among which alginate is used frequently.[115] Liu *et al.*[116] prepared 200–500 nm chitosan–sodium alginate nanoparticles with a spherical shape to deliver ε-polylysine, and *in vitro* release studies exhibited an initial burst release of ε-polylysine from the nanoparticles and then a sustained release. In addition, gum Arabic,[117] carboxymethyl cellulose,[118] pectin,[119] dextran sulfate,[120] and carrageenan[121] have also been commonly studied to prepare PEC nanoparticles with chitosan.

3.2 Chitosan microparticles/microspheres

Microspheres are spherical microparticles of between 1 and 1000 μm in size.[122] In order to fabricate chitosan microspheres, numerous methods have been reported. Firstly, spray drying is a well-developed method to produce the agglomerate, granule and powder forms of chitosan microspheres. Using this method, the initial step is to dissolve or suspend the polymer(s) and substances to be encapsulated in a liquid; then, the liquid is sprayed out in a stream of hot air to form the atomic size of the droplets.[123–125] Based on the nozzle size and discharge pressure, the particle size of the microspheres is typically in the range of 2–5 μm, and the form of the free-flowing powder contributes to carrying bioactive compounds.[126–128]

The second method is ionotropic gelation/PEC, similar to the methods for forming nanoparticles. Also, the polyanions used can be divided into two categories: low-molecular-weight counterions, such as TPP[129] and lauryl sulfate,[130] and high-molecular-weight counterions, such as polyaldehydrocarbonic acid,[131] κ-carrageenan[131] and alginate.[132] Briefly, acidified chitosan solution is extruded dropwise into magnetically stirred aqueous counterions and then filtered, washed with distilled water and dried to obtain the microspheres.[133] It has been reported that the polymer ratio, the DDA of chitosan, the molecular weight of the polymers, and the concentration of counterions significantly affect drug release from microspheres.[134,135]

The emulsion cross-linking method is different from the above three methods. Using this method, chitosan solution at a slightly acidic pH is added to liquid paraffin containing a surfactant, generating a water/oil emulsion before adding a cross-linking agent, after which the microspheres can be obtained by filtration, washing with a suitable solvent, and drying.[131] Generally, genipin,[136] formaldehyde[137] and glutaraldehyde[138] are the most commonly used cross-linkers for chitosan. Pahuja *et al.*[139] investigated the effect of six different cross-linking agents, including glutaraldehyde, formaldehyde, citric acid, vanillin, epichlorohydrin (ECH), and sulphuric acid, on chitosan microspheres loaded with losartan potassium. The results showed that, only when glutaraldehyde was used as the cross-linking agent, could the optimal formulation be achieved, where the percentage yield, average particle size, drug content, and entrapment efficiency

were 94.67%, 51.19 μm, 44.38 mg and 88.77%, respectively. They also found that as the concentration of the cross-linking agent was increased, a more rigid network structure was formed to retain more drug molecules for slower release.

3.3 Chitosan hydrogels. Hydrogels are commonly referred to as three-dimensional network structures that swell but maintain their structural integrity in aqueous solution. The preparation of hydrogels is mainly divided into two groups, physical and chemical modification.[140]

Generally, the physical modification of chitosan hydrogels is acquired *via* the interaction of non-covalent bonds, which include hydrogen bonds, electrostatic interactions, and hydrophobic interactions without the addition of cross-linking agents.[141] Because non-covalent bonds can be cleaved under physiological conditions, physically cross-linked hydrogels have good biodegradability.[142] Polymer blending is a promising method to provide chitosan with newly added properties that cannot be achieved using chitosan alone.[143] Freeze-thawing is a widely used physical method to produce hydrogels from a blend of chitosan and another polymer(s). Specifically, this method usually mixes polymers in an aqueous solution and then repeatedly freezes and thaws to promote the physical interaction between the polymer chains. Figueroa-Pizano *et al.*[144] prepared chitosan–poly(vinyl alcohol) (CS–PVA) hydrogels through repeated freezing and thawing, sustained by the hydrogen bonds between them. The CS–PVA hydrogels have been proved to have no cytotoxic effect on human cells and no erythrocyte aggregating and hemolyzing effect *in vitro*.[145] Similarly, ionotropic gelation/PEC is another technique for producing chitosan hydrogels, where cross-linking is usually achieved using polysaccharides, small anionic molecules, and metallic anions.[140] The most widely used anions for cross-linking chitosan are sodium alginate,[146] polyacrylic acid,[147] heparin,[148] and polyglutamic acid.[149] Wu *et al.*[150] prepared hydrogels based on chitosan and sodium alginate *via* electrostatic interactions for the delivery and protection of lysozyme. The relative activity of the lysozyme released from the chitosan/alginate hydrogels was up to 87.72 ± 3.96% of native lysozyme, and such hydrogels demonstrated effective inhibition against the growth of food-borne microorganisms by disrupting their basement membrane. While the challenge of electrostatic interactions is to control the ion diffusion to obtain a homogeneous material, hydrogels formed *via* this method possess improved physicochemical properties, such as mechanical stability, improved structural strength, and increased stability in swelling media at various pH values.[151]

Different from physical cross-linking, hydrogels formed using chemical methods have enhanced properties, including improved encapsulation efficiencies, excellent release profiles for bioactive delivery, and fortification.[151] Glutaraldehyde,[152] ethylene glycol diglycidyl ether (EGDE),[153] and ECH[154] are the most commonly used chemical cross-linkers for the preparation of chitosan hydrogels. The cross-linking mechanism of glutaraldehyde and EGDE is different from that of ECH. Glutaraldehyde and EGDE react mainly with amino groups instead of hydroxyl groups, while ECH is more likely to target the hydroxyl groups than amino groups.[151] As early as 2013, the effect of different amounts of glutaraldehyde as a cross-linker on the preparation of chitosan hydrogels has been well studied.[152] The interaction between one polymer and another was characterized, and they found that the concentration of glutaraldehyde was inversely proportional to the swelling ratio of the hydrogels. The results also showed that glutaraldehyde at a suitable concentration could reduce thermal effects and chain flexibility, proving that glutaraldehyde can make hydrogels stable. Another study reported that, using ECH as a cross-linking agent, chitosan/carrageenan hydrogels were fabricated.[155] The results exhibited that the composite hydrogels had a hierarchically porous architecture, great mechanical properties, and excellent responsiveness to pH and salts. Besides, *in vitro* studies using ATDC5 cells demonstrated that the proposed hydrogels enhanced the cellular adhesion and viability and induced chondrogenic differentiation of these cells. Apart from chemical cross-linking, grafting is another frequently used chemical method for imparting tailored properties to chitosan *via* the free amine and hydroxyl groups.[156] Based on these two reactive groups, chemical-grafting and radiation-grafting methods have been devised to modify chitosan hydrogels. As for chemical grafting on chitosan, this is usually initiated by generating at least one free-radical on the chain and allowing it to react with polymerizable monomers, which builds the grafted chain.[157] In recent years, numerous initiators such as ammonium persulfate,[158] ceric ammonium nitrate (CAN),[159] and potassium persulfate[160] have been applied to initiate grafting copolymerization. Jung *et al.*[161] employed CAN as an initiator to fabricate eugenol-grafted chitosan hydrogels, and they found that the anti-oxidative activities were enhanced and sustained. Compared with chemical grafting, radiation grafting is initiated *via* gamma rays or electron beams of high energy,[156] and is free of toxic additives.[162] Using the gamma-ray irradiation method, Taş delen *et al.*[163] synthesized chitosan/hyaluronic acid/hydroxyapatite hydrogels with significantly improved capacities of adsorption and drug release.

4. Preparation of chitosan-based oral colon-specific delivery systems

In Section 3, various methods for the preparation of chitosan-based carriers were well documented, which proved that these carriers can improve the delivery efficiency of bioactive compounds. Subsequently, chitosan has been widely applied for fabricating OCDS to deliver bioactive compounds with enhanced bioactivity,[164] because the biodegradability of chitosan could be utilized to design a microbe/enzyme-dependent OCDS, and at the same time, the mucoadhesion of chitosan is outstanding. Nevertheless, chitosan is soluble in aqueous systems with pH values below its pK_a (around 6.3),[165] which means that chitosan can be easily solubilized in gastric juice and the OCDS may thus lose its structural integrity. Hence, using a single physical or chemical modification method as discussed above, chitosan-based carriers can often fail to serve as an OCDS to overcome the complex environment of the upper GIT for delivery of compounds to the

colon. It is necessary to combine two or more preparation methods, as well as applying an enteric coating, to enhance the properties of chitosan, such as its swelling capacity, mechanical strength, *etc.*,[166] as summarized in Table 2. The most commonly used steps, ionotropic gelation or/and polyelectrolyte complex (a, b, or c), and coating (d), are shown in Fig. 4.

5. Chitosan-based oral colon-specific delivery systems for the delivery of polyphenols

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is the main natural polyphenol found in the rhizome of turmeric (*Curcuma longa* L., Zingiberaceae).[167] With potent anti-oxidative, anti-inflammatory, anti-microbial and anti-cancer effects, curcumin has been widely studied for the prevention of various illnesses ranging from IBD, cardiovascular diseases, and diabetes to CRC.[168–171] Similarly, (*trans*)-resveratrol ((*trans*)-3,5,4′-trihydroxystilbene) is a natural polyphenolic phytoalexin that exists widely in grape skin, and quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a typical flavonoid extracted from lettuce, peppers, and onions, which also have the wide health benefits.[172,173] To improve the bioactivity of these polyphenols, a chitosan-based OCDS has been explored extensively according to the mentioned principles, summarized in Table 2 from 2013 to 2022.

5.1 Chitosan-based nanoparticles with enteric coating

Chitosan-based positively charged nanoparticles can easily bind to the negatively charged cell membrane, and then enter the cell mainly through endocytosis, which promotes the absorption of encapsulated compounds.[174,175] In particular for tumor tissue, nanoparticles take advantage of the enhanced permeability and retention effect (named the EPR effect) to accumulate in tumors passively.[176] After being loaded on self-assembled chitosan nanoparticles (CS-NPs-CUR), curcumin was indeed taken up to a greater extent by colorectal cancer cells compared with the free form, resulting in a greater reduction in cell viability as well as a lower IC_{50}, indicating a potentially improved treatment outcome.[177,178] Furthermore, the application of pH-dependent OCDSs using Eudragit® S 100 or Eudragit® FS 30D for delivering curcumin chitosan-based nanoparticles has been explored by Khatik *et al.*[179] and Raj *et al.*,[180] respectively, to overcome the sensitivity of chitosan to acid. As a result, an *in vitro* release study showed that no curcumin release from coated CS-NPs-CUR was observed in SGF (pH 1.2), confirming the retention effect in an acidic environment, and a gamma-scintigraphic evaluation revealed good colon-specific targeting in mice. Similarly, thiolated-chitosan-based nanoparticles coated with Eudragit® S100 were developed to simultaneously deliver resveratrol and α-mangostin, leading to their synergistic activity against colon cancer cells.[181] Other sustained-release coated films are named Eudragit® RL and Eudragit® RS.[53] An *in vitro* experiment showed that the percentage of drug released from Eudragit® RLPO nanoparticles with different drug loads in 6 h was *ca.* 30%, and in 24 h was within the range of 72–93%.[182] The combination of the two different kinds of Eudragit® coating could establish a pH/time-dependent OCDS to improve drug release, which was explored in the administration of budesonide using Eudragit® FS 30D/Eudragit® RS 100,[183] and it is worth looking forward to delivering polyphenols better.

5.2 Modified chitosan-based nanoparticles

In addition to coating strategies, another approach used to prevent the rapid solubilization of chitosan in gastric acid is to apply different modifications. The physical combination of chitosan with other natural polysaccharides could improve its integrity and stability under different conditions,[184] where PEC with ionotropic gelation is the commonly used preparation method. A type of PEC prepared with chitosan and pectin containing curcumin (CS-pectin-NPs-CUR) was fabricated *via* mixing the two at pH 5 where electrostatic interactions between the positively charged amino groups of chitosan and the negatively charged carboxylic acid groups of pectin occurred, followed by the addition of TPP as the ionotropic gelated cross-linking agent.[185–188] The oral bioavailability of curcumin in CS-pectin-NPs-CUR was enhanced significantly by 4-fold after 6 h of treatment compared with free curcumin. The *in vitro* release experiment confirmed that negligible leaching of curcumin from CS-pectin-NPs-CUR was observed at pH 1.2 and pH 6.8, and pectinase in SCF (pH 7.4) played a key role in the release of curcumin *via* randomly catalyzing the cleavage of the α-1,4-glycosidic linkages of pectin to break existing bond formation between pectin and chitosan, suggesting pH/microbe-dependent behavior.[185] Also, the preparation of CS-pectin-NPs could be achieved by the combination of PEC and ionotropic gelation using $ZnCl_2$, with further optimization by adding polyethylene glycol (PEG), where the smaller size and larger surface area of the nanoparticles in the presence of PEG achieved 71.2 μM of loaded resveratrol reaching the simulated colon, nearly a times higher than 36.2 μM in the absence of PEG.[189]

The structural modification of chitosan *via* chemical, radiation, and enzymatic methods can also prevent its solubilization in the upper GIT to achieve colon-specific delivery.[190,191] Besides, structural modification can enable new functionalities of chitosan. The grafting of arginine to the nitrogen atom of chitosan improved the tight-junction opening ability of chitosan. Then, self-assembled nanoparticles from arginine–chitosan and thiolated fucoidan remained compact and stable at pH 2.0, and successfully improved the paracellular and transcellular delivery of curcumin across Caco-2 cell monolayers, suggesting a further increase in the curcumin bioavailability.[192] More importantly, structural modification can enable chitosan-based carriers to be more specific to the conditions of colon disease, expanding their responsiveness to pH and microbes. Chemotherapy is the common therapeutic approach used to treat cancers, such as the use of 5-fluorouracil for CRC.[193] A major problem with such treatment is that the drugs simultaneously affect cancerous and healthy cells, leading to depressing adverse effects.[194] Therefore, in addition to developing specific drugs, a more convenient and economical method is to develop specific drug-delivery systems for targeting cancer cells based on the membrane-anchored

Table 2 Overview of chitosan-based oral colon-specific delivery systems to deliver polyphenols from 2013 to 2022

Formulation	Active compound	Stimulus condition	Preparation technique[#]	Colon targeted performance*	Ref.
Nanoparticles					
Eudragit® S 100 coating, chitosan core	Curcumin	pH, microbe/enzyme	Ionic gelation, coating: emulsification solvent evaporation technique	• *In vitro* release: SGF (pH 1.2, 2 h), 0%; SIF (pH 7.4, +4 h), *ca.* 30%; SCF containing 4% rat cecal contents (pH 6.8, +18 h), 69.3 ± 6.4%. • *In vivo*, FITC-fluorescent points could be observed in the connective axis of the villi representing Eudragit S 100 coated CS-NPs inside vascular structures. • The pharmacokinetics proved a higher bioavailability of CUR in Eudragit S 100 coated CS-NPs compared with CUR in CS-NPs and free CUR.	179
Eudragit® FS 30D coating, chitosan core	Curcumin	pH, microbe/enzyme, mucoadhesion	Ionic gelation, coating: emulsification solvent evaporation technique	• *In vitro* release: SGF (pH 1.2, 2 h) + (SGF + SIF) (pH 4.5, +2 h) + SCF (pH 6.8, +1 h), 0%; SCF (pH 7.4, +19 h), 71.3 ± 2% *vs.* without 5% w/v rat cecal contents. • *In vivo*, the gamma-scintigraphic evaluation showed the Eudragit® FS 30D coated CS-NPs-CUR appeared in the colon at 8 h after oral administration.	180
Eudragit® S 100 coating, thiolated-chitosan core	Resveratrol, α-mangostin	pH, mucoadhesion	Chemical modification, ionic gelation, coating: emulsification solvent evaporation technique	• *In vitro* release: SGF (pH 1.2, 2 h), 0%; SIF (pH 6.8, +4 h), *ca.* 40% of α-mangostin and resveratrol; SCF (pH 7.4, +16 h), *ca.* 70% of α-mangostin and 80% of resveratrol. • Containing resveratrol and α-mangostin had the synergistic effect of inhibiting the activity of HT-29 and Caco-2 cells.	181
Chitosan/pectin	Curcumin	pH, microbe/enzyme, mucoadhesion	Polyelectrolyte complex, ionotropic gelation	• At pH 1.2 (6 h) and 6.8 (6 h), a slight swelling and negligible leaching of CUR from CS-pectin-NPs were observed. • At pH 7.4 with pectinase (6 h), a burst release of 15% of CUR was obtained in the first 20 min due to cleavage of the α-1,4-glycosidic linkages of pectin breaking the existing bond formation between pectin and chitosan by pectinase, and a plateau was manifested in 5 h with more than 80%. • The CS-pectin-NPs-CUR was taken up by HT-29 cells, ultimately resulting in a significant reduction in cancer cell propagation. • The oral bioavailability of CUR in CS-pectin-NPs was enhanced significantly by 4-fold after 6 hours of treatment compared with free CUR.	185 and 186
Chitosan/modified pectin	Curcumin	pH, microbe/enzyme mucoadhesion, ligand/receptor (cancer)	Polyelectrolyte complex, ionotropic gelation	• Overexpression of EGFR has been reported in colorectal cancer cells, and cetuximab is one of the anti-EGFR monoclonal antibodies. • In pH 1.2, only 19.74 ± 0.37% of CUR was released after 2 h; at the end of 24 h, 63.79 ± 0.66% was released in the cecal medium. • Cellular uptake studies displayed enhanced internalization of nanoparticles in Caco-2 (EGFR +ve) cells, which ultimately resulted in a significant reduction in cancer cell propagation.	187 and 188
Chitosan/pectin	Resveratrol	pH, microbe/enzyme	Polyelectrolyte complex, ionotropic gelation	• The release rate in SIF (pH 6.8) and SCF (pH 7.4) was faster than that in SGF (pH 1.2). • The release degree in SCF (pH 7.4) with pectinase was higher than without pectinase.	189
Folic acid–chitosan	*trans*-Resveratrol	Mucoadhesion, ligand/receptor (cancer)	Chemical modification, solvent evaporation method, hot homogenization method	• The solid lipid nanoparticles had good stability under the acidic conditions. • Cancer cells tend to overexpress FA receptors, thereby causing site-specific delivery of FA-conjugated nanoparticles. • The *trans*-resveratrol contained by FA-chitosan solid lipid nanoparticles effectively involved and increased cytotoxicity in HT-29 cells, leading to induction of apoptosis compared with free *trans*-resveratrol.	197

Table 2 (*continued*)

Formulation	Active compound	Stimulus condition	Preparation technique[#]	Colon targeted performance*	Ref.
Microparticles/microspheres					
Eudragit® S 100 coating, chitosan core	Ellagic acid	pH, microbe/enzyme, mucoadhesion	Emulsion cross-linking, coating: emulsification solvent evaporation technique	• *In vitro* release: pH 1.2 (2 h) + pH 6.8 (+2 h), 8%; pH 7.4 (+20 h), 55% in the first 2 h and *ca.* 85% at the end. • The formula exhibited enhanced cytotoxic and proapoptotic activity against HCT 116 cells compared with the administration of raw ellagic acid.	218
Eudragit® S 100 coating, thiolated-chitosan/alginate core	Curcumin, 5-aminosalicylic acid	pH, mucoadhesion	Chemical modification, polyelectrolyte complex, ionotropic, gelation coating: emulsification solvent evaporation technique	• *In vitro* release: SGF (pH 1.2, 1 h) + simulating duodenum fluid (pH 4.5, +2 h), 0%; SIF (pH 6.8, +2 h), *ca.* 4.35% of 5-aminosalicylic acid and 6.37% of CUR; SCF (pH 7.4, +43 h), *ca.* 76.5% of 5-aminosalicylic acid and 73.9% of CUR in the first 7 h. • *Ex vivo* mucoadhesive tests showed that the microparticles have excellent mucosal adhesion for the colonic mucosa of rats benefitting from the immobilized thiol groups. • The microparticles showed superior therapeutic efficiency for the UC rats induced by TNBS.	219
Eudragit® S 100 coating, chitosan core	Curcumin, ascorbic acid	pH, microbe/enzyme, mucoadhesion	Ionic gelation, spray-drying coating,: emulsification solvent evaporation technique	• *In vitro*, the Eudragit-coated formulations released a negligible quantity of CUR (total 5%) at pH 1.2 (2 h) + pH 4.5 (+2 h); thereafter, the release rate was increased at pH 6.8 (+20 h). • *In vivo*, after 6–8 h of administration, a maximum percentage of CUR was observed in the colon.	220
Eudragit® S 100 coating, chitosan core	Curcumin	pH, microbe/enzyme	Emulsion cross-linking, coating: emulsification solvent evaporation technique	• Eudragit coating of chitosan microspheres prevented the premature release of CUR in the upper GIT, and the release rate was found to increase at pH 7.4. • *In vivo* organ biodistribution study showed a negligible amount of CUR in the stomach and small intestine. • *In vivo* study revealed a significant reduction in severity and extent of colonic damage with CUR-loaded microspheres compared with pure CUR.	221
Capsugel® DRcaps™ acid-resistant capsules coating, chitosan core	Quercetin	pH	Ionic gelation, coating: not shown	• *In vitro* release: SGF (pH 1.2, 2 h) + SIF (pH 6.8, +2 h), 18.1 ± 1.3%; healthy SCF (pH 7.2, +24 h), 75.7 ± 5.8%, or inflammatory SCF (pH 4.2, +24 h), 93.6 ± 2.65% in the first 10 h. • The animals treated with quercetin microparticles had significantly improved therapeutic outcomes.	222
Chitosan/alginate	Mangostin	pH, microbe/enzyme	Polyelectrolyte complex, ionotropic gelation	• *In vitro* release: SGF (pH 1.2, 3 h), *ca.* 45%; SIF (pH 7.4, +4 h), *ca.* 55%; SCF (pH 6.8, +3 h), 100% (Formula 10).	223
Chitosan/alginate	Icariin	pH, microbe/enzyme	Polyelectrolyte complex, ionotropic gelation, emulsion cross-linking	• *In vitro* release: pH 1.2 (2 h), *ca.* 8%; pH 6.8 (+3 h), *ca.* 40%; pH 7.4 (+24 h), *ca.* 65%. • The fluorescence tracer indicated high retention of targeted microspheres for more than 12 h in the colon. • The microspheres loaded with icariin decreased the colon mucosa damage index and the inflammatory response to prevent the colonic mucosal injury induced by TNBS/ethanol in rats.	224

Table 2 (*continued*)

Formulation	Active compound	Stimulus condition	Preparation technique[#]	Colon targeted performance*	Ref.
Hydrogels					
Chitosan/alginate/pectin	Ellagic acid	—	Polyelectrolyte complex, ionotropic gelation, electro-sprayed	• *In vitro* release: SGF (pH 1.2, 2 h), 0%; SIF (pH 6.8, +3 h), 18%.	225
Chitosan as the coating					
Chitosan/Nutriose coating, liposome core	Quercetin	Microbe/enzyme	Polyelectrolyte complex	• The release of quercetin in coated liposomes was ∼22% in SGF (pH 2, 2 h), ∼30% in SIF (pH 5.5, 3 h) and ∼80% in SCF (pH 7, 8 h), lower than that in uncoated liposomes during all three phases. • The chitosan/Nutriose-coated liposomes improved the quercetin accumulation in the colon, allowing it to exert its local anti-oxidative and anti-inflammatory action there, thereby reducing the colon damage and permitting an important amelioration of the TNBS-induced UC symptoms.	230
Chitosan/Nutriose coating, liposome core	Rosmarinic acid	Microbe/enzyme	Polyelectrolyte complex	• The chitosan/Nutriose-coated liposomes increased rosmarinic acid local bioavailability in the colon. • The chitosan/Nutriose-coated liposomes could protect the colonic mucosa against DSS-induced damage by attenuating inflammation and oxidative stress by modulating the NLRP3 inflammasome and re-establishing the Nrf2/HO1 signaling pathway.	231
Chitosan/alginate coating, chondroitin sulfate-chitosan/PLAG core	Curcumin	pH, ligand/receptor (inflammation)	Polyelectrolyte complex, ionotropic gelation	• Chondroitin sulfate exhibits a strong affinity with glycoprotein CD44 that is highly over-expressed on the surface of macrophages in the inflamed colon. • *In vivo*, the coating of chitosan/alginate prevented damage of the nanoparticles during their passage through the upper GIT and further released them into the colonic lumen. • *In vitro* and *in vivo* experiments proved that chondroitin sulfate functionalization could enhance the accumulation of nanoparticles in macrophages in inflammatory tissues, achieving better therapeutic outcomes against UC.	233
Chitosan/alginate/chitosan coating, PLAG core	Resveratrol	pH, charge (inflammation)	Polyelectrolyte complex (layer by layer)	• *In vitro* release: SGF (pH 1.2, 2 h) + SIF (pH 6.8, +3 h), *ca.* 25%; SCF (pH 7.4, +31 h), *ca.* 50%. • Fluorescence imaging of colitis tissue showed stronger fluorescence accumulation in the DSS-treated UC mice than in the normal group due to the charge-reversal properties of nanoparticles. • Oral nanoparticle treatment in DSS-induced mice significantly improved inflammatory markers of UC.	234
Chitosan/alginate coating, chondroitin sulfate-silk fibroin core	Curcumin	pH, GSH, ROS ligand/receptor (inflammation)	Polyelectrolyte complex, ionotropic gelation	• Chondroitin sulfate as a specific receptor for CD44 could be used to functionalize nanoparticles to be recognized by activated macrophages residing in the colitis tissue, which was proven by the cellular uptake experiments using Raw 264.7 macrophages. • Silk fibroin has the intrinsic capacity to respond to GSH and ROS due to the functional groups (amino groups and disulfide bonds) as well as β-sheet structures; thus, *in vitro* experiments showed accelerated drug release behaviors in H_2O_2 (or GSH)-contained buffers. • The nanoparticles accumulating in the colitis tissue remarkably alleviated UC symptoms, maintained the homeostasis of intestinal microbiota, and improved the survival rate of mice.	204
Chitosan/alginate coating, cyclodextrin core	Curcumin	pH, microbe/enzyme	Polyelectrolyte complex, ionotropic gelation	• *In vitro* release: SGF (pH 1.2, 2 h), 12%; SIF (pH 6.8, +2 h), 27%; SCF (pH 7.4, +8 h), *ca.* 55% without α-amylase but 100% with α-amylase.	239

Table 2 (*continued*)

Formulation	Active compound	Stimulus condition	Preparation technique#	Colon targeted performance*	Ref.
				• After 12 h of administration, the FITC fluorescence intensity presenting nanoparticles was strong in the colon, with the promotion of colonic epithelial barrier integrity, the modulation of inflammatory cytokines production, and the remodeling of gut microbiota in mice with DSS-induced UC.	
Chitosan/alginate coating, hyaluronic acid/L-arginine CO_2 core	Pterostilbene	pH, ligand/receptor (inflammation)	Polyelectrolyte complex, ionotropic gelation	• Hyaluronic acid could specifically target the CD44 receptor overexpressed 240 on macrophages and colonic epithelial cells during UC. • *In vitro* and *in vivo* experiments proved that hyaluronic acid functionalization could enhance the accumulation of nanoparticles in macrophages in colitis tissues, yielding significant outcomes in alleviating UC symptoms.	

"—" means "not mentioned in the text". # The preparation technique in "*Chitosan as the coating*" only focused on the preparation of chitosan coating, not on the core. * Abbreviation: *circa*, *ca.*; chitosan, CS; curcumin, CUR; dextran sulfate sodium, DSS; EGFR, epidermal growth factor receptor; folic acid, FA; gastrointestinal tract, GIT; nanoparticles, NPs; simulated gastric fluid, SGF; simulated intestinal fluid, SIF; simulated colonic fluid, SCF; 2,4,6-trinitrobenzenesulfonic acid, TNBS; ulcerative colitis, UC.

ligand/receptor principle.[195] The overexpression of folic acid receptors in cancer cells compared with normal cells makes it a potential target.[196] Correspondingly, Senthil Kumar *et al.*[197] designed chitosan-coated solid lipid nanoparticles conjugated with folic acid to deliver *trans*-resveratrol and ferulic acid with good stability under acidic conditions and with increased cytotoxicity in HT-29 cells. Other ligand-conjugated nanoparticles for CRC treatment have been reviewed by Cisterna *et al.*,[198] and for IBD-relevant ligand/receptors (*e.g.*, mannose receptor, CD98, CD44, and ICAM-1), Liu *et al.*[88] have made a comprehensive summary. In addition, IBD is furthermore accompanied by the over-accumulation of reactive oxygen species (ROS)[199] and glutathione (GSH)[200] inside the inflammatory cells. Representative ROS-sensitive linkers include thioethers, selenides/tellurides, diselenides, thioketals, arylboronic esters, *etc.*,[201] while GSH-responsive linkers mainly contain disulfide bonds such as lipoic acid.[202] Excitingly, the functional groups of chitosan, *i.e.*, amine and hydroxyl groups, have the ability to combine with the above linkers, and this application has been reviewed by Sabourian *et al.*[203] All of these studies could guide the delivery of polyphenols in the future, and the application of multi-targets is considered as a promising strategy for designing OCDSs that integrate the specific aggregation (a), uptake (b), and release of drugs (c) (Fig. 5), which has been referenced by some researches[204,205] to deliver polyphenols to the colon.

5.3 Chitosan-based microparticles/microspheres and hydrogels

There is no doubt that polyphenols have a wide range of biological activities. However, less than 5–10% of the total polyphenolic intake is absorbed and reaches the plasma unchanged, without efficient cellular concentrations to justify the overall efficacy.[206] The low bioavailability/high bioactivity paradox draws attention to gut microbial metabolites that can pass easily into the systemic blood circulation from the rest of 90–95% dietary polyphenols.[207] Several reviews have been published to report that many metabolites exhibited similar or even higher biological effects compared with the parent compounds, including curcumin, (*trans*)-resveratrol and quercetin.[208–210] The most widely studied is urolithin A, the microbial metabolite of ellagic acid, which shows a protective effect on the intestine[211] and beyond.[212–214] In other words, these polyphenols act like a prodrug similar to sulfasalazine. Conversely, polyphenols could also act as prebiotics to regulate intestinal flora homeostasis and play a huge role in systemic health.[215] Therefore, we expect to increase the retention time of polyphenols in the colonic lumen, maximizing the benefits of the reciprocal relationship between polyphenols and microorganisms (Fig. 6). The significance of prolonging the retention time of polyphenols in preventing IBD has been proved by Hu *et al.*[216] using a hydrogel carrier. As mentioned above, the luminal side of colonic epithelial cells is covered with mucus, which can interact with chitosan *via* electrostatic attraction, hydrogen bonding, and hydrophobic effects to achieve a long retention time in the colon.[217] Considering the <200 nm pore size of the mucus net,[71] the microparticles/microspheres and

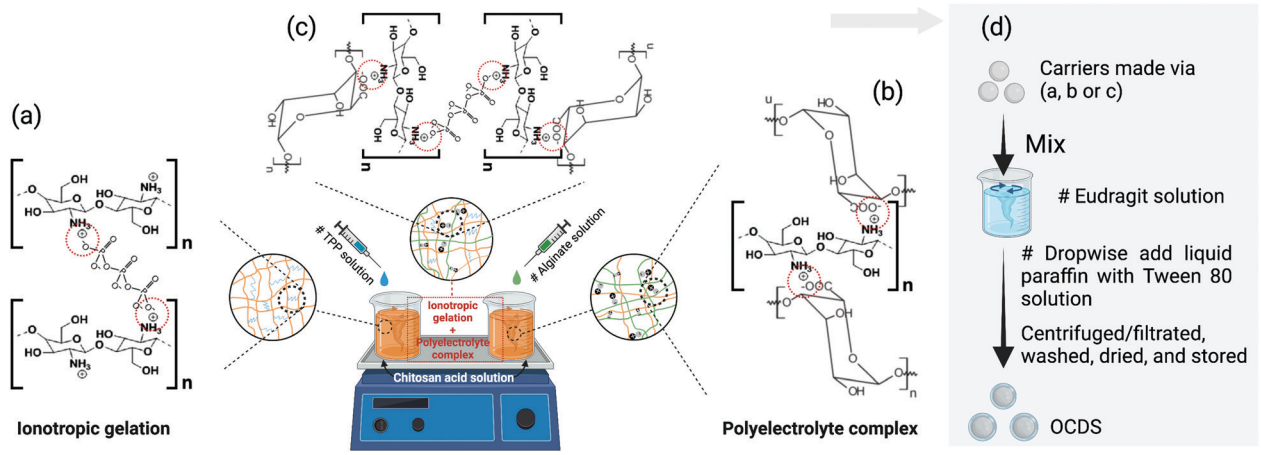

Fig. 4 Common steps that are used to prepare chitosan-based colon-specific delivery systems, including (a) ionotropic gelation, (b) polyelectrolyte complex, (c) the combination of ionotropic gelation and polyelectrolyte complex, and (d) coating. The content labeled with "#" could be alternative with other small anionic molecules (ionotropic gelation), anionic macromolecules (polyelectrolyte complex) and coating materials. The figure was created using BioRender (https://biorender.com/).

hydrogels with large sizes are the ideal carriers, compared with nanoparticles.

Similar modification strategies discussed for the chitosan-based nanoparticles have also been explored for designing mucoadhesive chitosan microparticles/microspheres and hydrogels as OCDSs for polyphenols. The coating agent, Eudragit® S 100, played a role in the intact passage of chitosan-based microparticles/microspheres through the gut and small intestine, involving the delivery of ellagic acid[218] and curcumin,[219–221] which were pH/microbe (enzyme)-dependent.[28] Duan *et al.*[219] even made thiolated chitosan to improve its mucoadhesion. Similarly, Capsugel® DRcaps™ acid-resistant capsules made from hydroxypropyl methylcellulose packaged the chitosan-based microparticles containing quercetin to cure IBD in rabbits.[222] Like pectin, alginate can be complexed with chitosan through strong electrostatic interactions between the negatively charged carboxylic acid groups of mannuronic and guluronic acid units in alginate and the positively charged amino groups of chitosan. Not surprisingly, the physical interaction between chitosan and alginate can help the colon-targeted delivery of mangostin[223] and icariin[224] *via* microparticles/microspheres, and ellagic acid *via* hydrogel beads.[225] Although there have been limited reports on the chitosan-based hydrogel as the

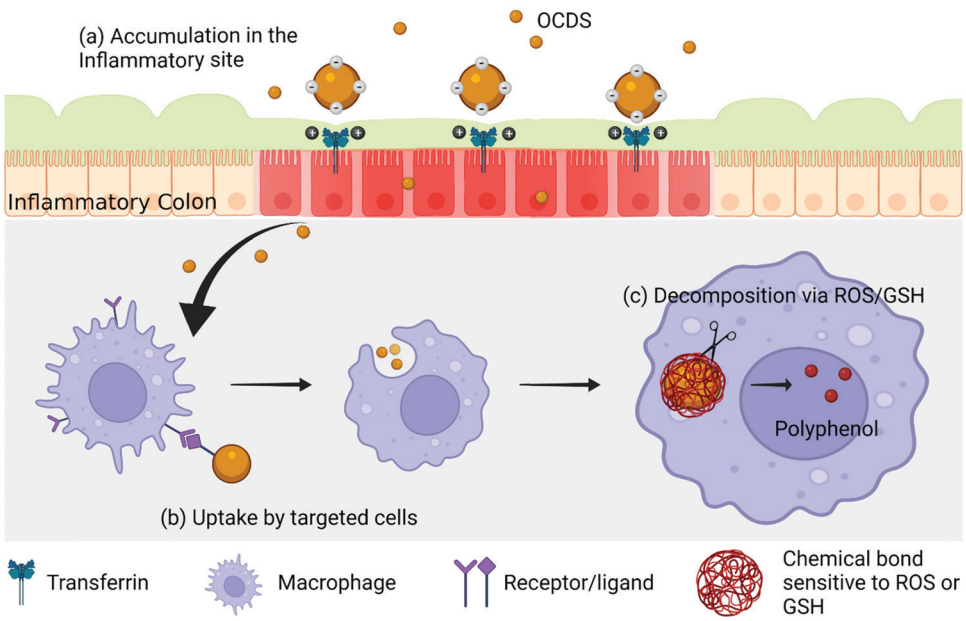

Fig. 5 Fate of polyphenols delivered *via* multi-responsive colon-specific delivery systems (nanoparticles) in the colon, as follows: (a) the carriers accumulate at the inflammatory site *via* electrostatic interactions; (b) the carriers are recognized *via* receptor/ligand patterns and taken up by macrophages; and (c) the carriers are decomposed *via* the action of ROS/GSH to release the polyphenols in the cell. The figure was created using BioRender (https://biorender.com/).

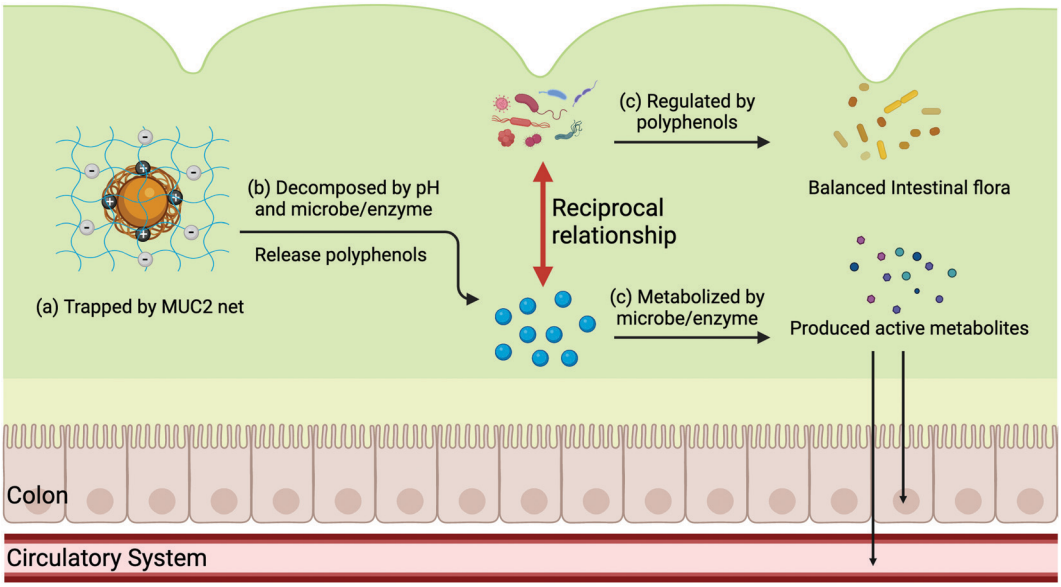

Fig. 6 Fate of polyphenols delivered *via* mucoadhesive colon-specific delivery systems (microparticles (microspheres)/hydrogels) in the colon, as follows: (a) the mucoadhesive carriers are trapped by the MUC2 net mainly *via* electrostatic interactions; (b) the trapped carriers are decomposed *via* the action of microbes/enzymes and pH to release the polyphenols; and (c) the released polyphenols are metabolized by microorganisms to produce active metabolites, and, in turn, the intestinal flora are regulated by the polyphenols to be homeostatic. The figure was created using BioRender (**https://biorender.com/**).

carrier itself in the OCDS, the design of the hydrogel coating for other carriers is mature (discussed below). Besides, polysaccharide-based hydrogels are potential carriers for the colon-targeted delivery of polyphenols;[45,226] thus, considering the development of chitosan hydrogels for sustained drug delivery,[227] their wider application in OCDSs is just a matter of time.

5.4 Chitosan as the coating material

Due to its film-forming properties, the complexation of chitosan with other polysaccharides could be used as a protective coating material, like Eudragit®, for various carriers, particularly nanoparticles. Liposomes are the most successful nano-drug carriers in current drug-delivery systems,[228] and a coating of chitosan has been developed to overcome the low resistance of conventional liposomes to gastric pH conditions and enzymatic degradation.[229] Furthermore, the chitosan coating can be modified by Nutriose®, a water-soluble and branched dextrin with a high fiber content, to acquire the promising ability to protect quercetin or rosmarinic acid during its transit through the upper GIT and enable its release in the colonic region due to the effect of microbes/enzymes.[230,231] Poly(lactic-*co*-glycolic acid) (PLGA) is one of the most effective biodegradable polymers, which has received US FDA approval for use in drug-delivery systems.[232] After depositing chitosan and alginate on the surface of PLGA nanoparticles, the loaded curcumin or resveratrol could smoothly reach the colon.[233,234] On the swelling mechanism of drug release, the gel coating of chitosan/alginate exhibits pH-dependent behavior.[235]

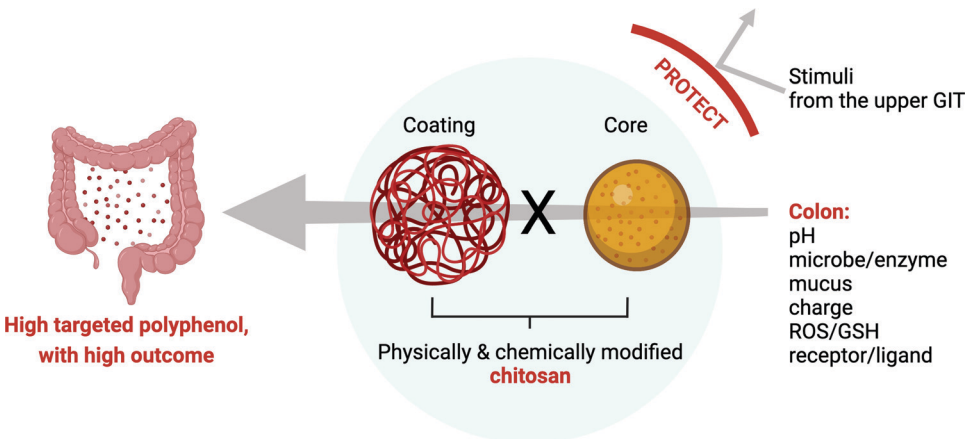

Fig. 7 Summary of a chitosan-based OCDS to deliver polyphenols. The figure was created using BioRender (https://biorender.com/).

Interestingly, it has been reported that inflammation of the colonic mucosa is accompanied by depletion of the mucus layer and the *in situ* accumulation of positively charged proteins, including transferrin,[236] which has been applied to develop an inflammation-targeting carrier with a negative charge for preventing IBD[45,237] (Fig. 5a). Thus, there is no doubt that the presence of alginate helps the carrier with curcumin or resveratrol to be concentrated at the site of inflammation in IBD mice.[234,238] In addition, the synergistic coating effect of chitosan/alginate on various nanoparticles for polyphenol delivery is unlimited, with different modified properties to further improve the targeting efficiency.[204,239,240] All in all, chitosan can be modified both physically and chemically, and can be used as a carrier itself or a carrier coating, which greatly expands its potential for the colon-targeted delivery of polyphenols, as reviewed in Fig. 7.

6. Conclusions and perspectives

OCDS is a promising tool for the delivery of ingredients that need to be protected from degradation/absorption in the upper GIT, thereby concentrating on the colonic site for health interventions. Chitosan is a ubiquitous natural polysaccharide derived from chitin, with tunable physicochemical properties that are suitable for chemical and physical modification to bring about resistance to the harsh environment of the upper GIT, followed by disintegration under stimulation in the colon. In this review, the factors in the GIT that influence the design of OCDSs have been systematically summarized (Fig. 2), and the preparation of chitosan-based carriers, including nanoparticles, microparticles/microspheres and hydrogels, has also been introduced, providing guidance for establishing chitosan-based OCDSs (Fig. 3 and 4). Besides, the delivery of polyphenols by chitosan-based OCDSs has been systematically summarized to shed light on further developments for nutritional and biomedical applications (Fig. 7).

Mucus is an important structural component of the colon, which can influence the biological fate of OCDSs. We must mention that both nanoparticles and microparticles (microspheres)/hydrogels are mucoadhesive (Table 2). However, in this review, it has been considered that pristine polyphenols and their metabolites all play important roles in human health. Due to the effect of their size, nanoparticles can achieve the delivery of intact polyphenols *via* cellular uptake, so we prefer to design nanocarriers in the direction of mucosal penetration with multiple responses (Fig. 5), while microparticles/microspheres and hydrogels tend to be trapped in the mucus to continuously release polyphenols so allowing them to be fully metabolized by microorganisms and regulate the intestinal flora homeostasis in turn, to exert their function (Fig. 6). Thus, it is important that scientists need to consider carriers with different geometries based on the nature of the polyphenol of interest and the purpose of the research when preparing chitosan-based OCDSs for polyphenol delivery.

Safety evaluations and clinical trials are essential steps before expanding the application of OCDSs to the market. Although both chitosan and polyphenols are biological materials, their safety for human beings still needs to be taken into account, especially considering the uncontrollable source and insufficient purity caused by imperfect preparation methods. Thus, the toxicity and immunogenicity of a chitosan-based OCDS containing polyphenols need to be fully investigated in the long term. So far, the conclusions from research have mainly been based upon *in vitro* or/and *in vivo* animal studies (mice/rats/rabbits). The effective construction of OCDSs relies heavily on differences in the parameters of each segment of the GIT, which may differ appreciably between animals and humans, leading easily to the failure of clinical translation. To bridge this gap, novel modifications of chitosan to enhance its broader resistance, or non-destructive chemical cross-linking between polyphenols and chitosan, might be the solution, which, however, appears to be a new challenge. Fortunately, there have already been some clinical trials on polyphenols[241] and chitosan carriers,[242] and clinical studies on OCDSs for gene delivery are also involved, which would guide us in the right direction.

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Author contributions

Sunni Chen: visualization, writing – original draft preparation; Honglin Zhu: conceptualization, writing – original draft preparation; Yangchao Luo: supervision, writing – review and editing supervision.

Conflicts of interest

The authors declare no conflict of interest.

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