

Considerations in excipient selection for colon-targeted dosage forms

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ABSTRACT

The colon is a potential organ for drug delivery systems because it has several advantages, such as long transit time and neutral pH conditions. Moreover, colon targeting can avoid enzymatic reactions in the stomach and small intestine which increase the bioavailability of the drug. A colon targeted drug delivery system (CDDS) requires excipients that have distinctive characteristics to prevent drug release in the upper gastrointestinal tract and enhance drug release in the colon. Polysaccharides are suitable in CDDS due to the degradation mechanism by colonic microflora enzymes. Furthermore, polysaccharides can swell when hydrated so that drugs can be released from the matrix system by diffusion and/or relaxation. Polysaccharides can swell when hydrated, which will form a gel-like matrix that enables drug release through diffusion, where the drug diffuses through the swollen matrix. Additionally, drug release can occur through a relaxation mechanism, where the polymer chains gradually unwind and erode, further facilitating the drug release. This degradation and swelling mechanism can lead to the release of the drug at the colon site. Some polysaccharides that can be utilized for CDDS are alginate, amylose, arabinoxylan, dextran, guar gum, inulin, carrageenan, chitosan, chondroitin sulfate, lactulose, locust bean gum, pectin, and cyclodextrin. Moreover, polymers can also be employed as excipients in CDDS due to conformation changes in different pH of the gastrointestinal tract. These pH-dependent properties can ensure that the drug is protected during transit through the stomach and small intestine and is only released when the dosage form reaches the colon. Some polymers that are potential for CDDS are cellulose derivatives, poly (acrylic acid) (PAA), poly (metha-acrylic acid) (PMAA), Eudragit®, poly (lactic-co-glycolic acid) (PLGA), Kollicoat®, and Shellac®. The combination and/or modification of these excipients can increase the effectiveness of CDDS and prevent the early release of drugs in the upper gastrointestinal tract which can lead to the drug release being more precisely controlled in the colonic site.

INTRODUCTION

The drug delivery system can deliver and release active pharmaceutical ingredients at the desired location at an appropriate rate, which can produce optimal therapeutic effects [1]. Nowadays, the most preferred route of administration is oral due to numerous advantages, such as easy administration, high patient compliance, and an inexpensive manufacturing process

[2]. However, oral drug administration also has some drawbacks, including the slow onset of action, first-pass metabolism, the possibility of degradation, stability of the drug in the gastrointestinal tract, and is influenced by gastric emptying time [3]. To overcome the drawbacks of oral administration, the colon is one of the potential drug absorption sites in the oral delivery system. The colon has a longer transit time, around 20 to 30 hours, compared to the upper gastrointestinal tract. Furthermore, the pH condition in the colon is around 6.0 to 7.5 which is a neutral pH for drug absorption [4]. In addition, a low enzyme activity in the colon may prevent the degradation of the drug [5]. High drug concentrations can be achieved in the colon, therefore increasing efficacy and reducing side effects [6].

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Drug delivery systems via the oral route targeted to the colon are currently being developed to deliver drugs with low bioavailability that can be administered both systemically and locally [7]. The colonic drug delivery system is an alternative for drugs that have low bioavailability, instability to pH, enzymes, low solubility, short half-life, and poor absorption [8]. Several developments of oral drug delivery systems targeted to the colon include those for delivering insulin [9,10], proteins [11], hormones [12], colorectal cancer [13,14], and drugs for inflammatory bowel diseases (IBDs) [15,16].

Several colon-targeted drug delivery systems (CDDSs) have been developed to control drug release so the drug will not be released at the upper gastrointestinal tract and improve drug efficacy [17], including pH-sensitive systems [18,19], time control systems [20], degradation systems by microflora in the colon [21], prodrugs [22], and osmotic systems [23]. From several approaches to CDDS, an excipient with unique characteristics is needed to protect drug release at the upper gastrointestinal tract and enhance drug release in the colon.

Polysaccharides have been widely used for CDDS through swelling and degradation by microflora present in the colon [4]. When the drug delivery system reaches the colon, polysaccharide-digesting enzymes are secreted by the colonic microflora to degrade the polysaccharides so that the drug can be released [24]. In addition, polysaccharides can also be used as prodrug carriers by targeting ligands and activation by enzymes in the colon so that the drug is not released before the drug reaches the colon [22]. Furthermore, polymers can be used to protect, delay, and control drug release [25]. The polymers used have pH-sensitive characteristics, which are resistant or insoluble at acidic pH but can be degraded when the pH becomes alkaline [26]. Polymers are also used to release drugs based on time so that drugs can be released in the colon [20,27].

Combining polysaccharides with water-insoluble polymers can control the development and/or solubility of polysaccharides so that drug release does not occur in the stomach and small intestine [17]. The combination of polysaccharides with water-insoluble polymers is often used to control the development and/or solubility of polysaccharides so that drug release does not occur in the upper gastrointestinal tract [17]. The use of a combination of excipients such as polysaccharides with enteric polymers can prevent burst effects in the stomach and small intestine and can increase the delay time and effectiveness of targeted drug delivery systems to the colon.

This review article will discuss the excipients that can be used for drug delivery systems targeted to the colon. The excipients to be discussed are classified based on the type or class of these excipients, including polymers and polysaccharides.

CHARACTERISTICS OF EXCIPIENTS USED FOR COLON DRUG DELIVERY SYSTEM

CDDS should control drug release and maintain drug concentration at the colon site [8]. Therefore, CDDS requires excipients that can protect the drug in the large intestine from degradation, release, and absorption before reaching the colon [4].

Polysaccharides

Polysaccharides are macromolecular compounds with large molecular weight, consisting of long chains of monosaccharide units (more than 10 monosaccharides) linked by glycosidic linkages. Polysaccharides can be used in CDDS because they can be degraded by enzymes from various microflora colonization in the colon [28]. Some of the microflora in the colon include *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Enterobacteriaceae*, *Lactobacillus*, *Bacillus subtilis*, *Peptococcus*, *Clostridium*, and *Escherichia coli* [29,30]. These microflora produce reductive and hydrolytic enzymes that can degrade polysaccharides, such as β -d-glucosidase, β -d-galactosidase, amylase, pectinase, xylanase, β -d-xylosidase, dextranase, glucuronidase, xylosidase, and arabinosidase [30,31].

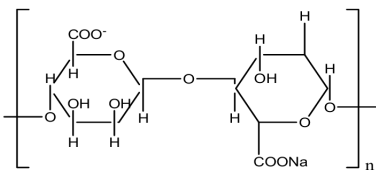
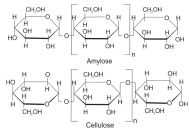
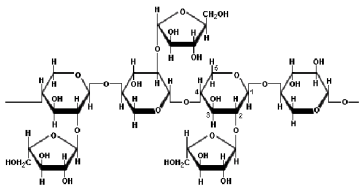
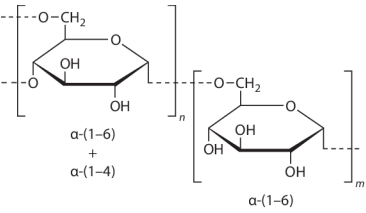
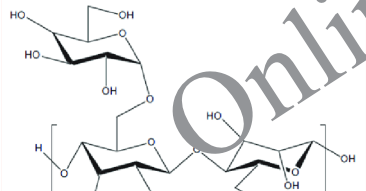
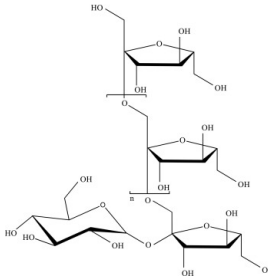
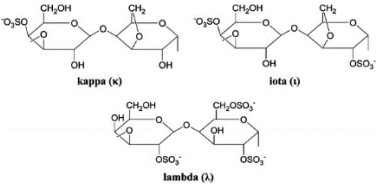
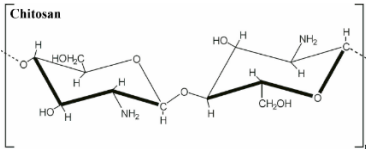
When the drug reaches the colon, the glycosidic bonds of the polysaccharides will be hydrolyzed by enzymes secreted by the colonic microflora, and the drug can be released in the colon [29]. Some mechanisms of polysaccharide degradation by microflora include a Starch utilization system (Sus)-like transport, ATP-binding cassette (ABC)-transport system, and cellulosome-like scaffolded enzyme system. The enzymes in the Sus-like transport system are encoded by the polysaccharide utilization loci (PUL) which are found in about 18% of the genome of *Bacteroides*, especially *Bacteroides thetaiotaomicron*. Lipoproteins SusD, SusE, and SusF degrade polysaccharides into maltooligosaccharides through SusG which is then carried into the cytoplasm through the TonB-dependent transporter SusC. Maltooligosaccharides will be degraded into maltose and glucose by α -glucosidase and neopululanase. Another mechanism of polysaccharide degradation is through the ABC-transport system in *Eubacterium rectale* which will degrade polysaccharides into maltooligosaccharides by the amylase enzyme on the cell surface. Maltooligosaccharides will be recognized by glycoside hydrolases and then transported to the cytoplasm in the form of maltose and glucose. The cellulosome-like scaffolded enzyme system in *Ruminococcus* unites cellulose and enzymes together on the cell surface through the dokerin protein to degrade cellulose into monosaccharides [32]. When the polysaccharides that coat the drug are degraded by enzymes produced by the microflora in the colon, the drug will be released from the system.

Another mechanism of drug release is that polysaccharide-based hydrogel particles can swell when water is absorbed with the increased size of the porous structure. The encapsulated drug can be released from the matrix system [33]. However, high polysaccharide concentrations form a thicker gel layer around the tablet when the polysaccharide expands, which may inhibit drug release [34]. Excipients of polysaccharides used for the CDDS can be seen in Table 1.

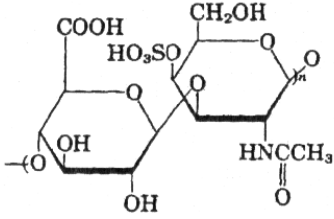
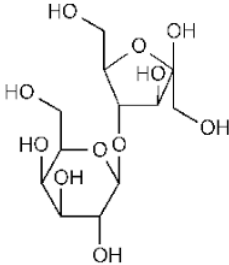
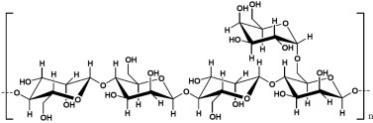
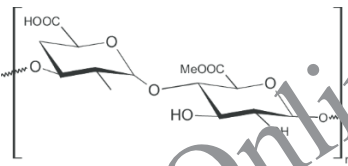
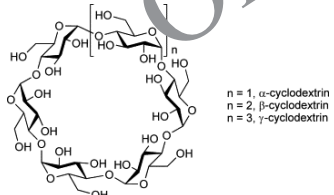
Alginate

Alginate is an anionic polysaccharide that contains negatively charged carboxylic groups at pH 5 and above. The alginate structure consists of α -1,4-l-guluronic (G) units and β -1,4-d-manuronic acid (M) from *Laminaria hyperborea*, *Macrocystis pyrifera*, and *Ascophyllum nodosum*. Alginate is available in the form of salts such as sodium alginate, and

Table 1. Excipients of polysaccharide used for CDDS.

Excipient	Structure	CDDS mechanism	Reference
Alginate		pH sensitive, mucoadhesive, degradation by colonic microflora	[35,36]
Amylose		Degradation and fermentation by colonic enzymes, Swelling	[37,38]
Arabinoxylan		Gel formation, fermentation by colonic microflora	[43,149]
Dextran		Prodrug conjugate, Hydrolysis by dextranase enzymes in the colon	[41,42]
Guar Gum		The development of the polymer matrix is induced by the relaxation of the matrix and the rate of water diffusion into the polymer matrix	[43,44]
Inulin		Degradation by inulinase secreted by <i>Bifidobacterium</i> in the colon	[45]
Carrageenan		Swelling, pH and pKa dependent	[46,47]
Chitosan		Swelling, pH sensitive, mucoadhesive, colonic degradation by enzymes, drug conjugates	[28,48,49]

(Continued)

Excipient	Structure	CDDS mechanism	Reference
Chondroitin Sulfate		Gel formation, Swelling, degradation by colonic chondroitinase, drug conjugates	[50-52]
Lactulose		CODEST TM , degradation by β -galactosidase secreted by <i>L. sporogenesis</i>	[53,54]
Locust bean gum		Swelling, degradation by β -mannanase, β -mannosidase and α -galactosidase	[55,56]
Pectin		Gel formation, degradation by pectinases, prodrug	[57,58]
Cyclodextrins		Prodrug, conjugate with drugs, degradation via hydrolysis reaction by α -amylase and carboxylesterase	[59,60]

calcium alginate. Alginates can form a stable gel in aqueous media, and with the addition of multivalent cations, such as calcium chloride, they can form cross-links to make a strong chemical bonding [61,62]. Alginates have low solubility in the stomach and small intestine but can dissolve and expand at alkaline pH in the colon. Alginates also have a mucoadhesive ability which allows for adherence to the colon. Under acidic pH, carboxylic acid groups do not dissociate, but at alkaline pH, carboxylic acid groups are converted into negatively charged carboxylic ions. This will produce electrostatic repulsion and swelling that cause drug release [30]. Alginate and its derivative compounds have been utilized for CDDS with pH-dependent and enzyme degradation mechanisms. Iswandana *et al.* [63] conducted a drug release study from tetrandrine-coated calcium alginate and cellulose acetate phthalate (CAP) which showed that 1.23% and 67.68% of

tetrandrine have been released in pH 1.2 and 6.8, respectively. Hence, this formulation can protect against burst release in acid pH and enhance drug release in colon conditions. The hydration of the hydroxyl groups of alginates influences calcium alginate swelling studies. The more ion Ca^{2+} bound to the alginate can increase the swelling degree [63]. In addition, Agarwal *et al.* [30] have successfully employed a combination of calcium alginate and carboxymethyl cellulose for the delivery of 5-Fluorouracil beads, which reported that the beads remained attached to the mucosal surface of the large intestine for 24 hours, but only 2–3 hours at acidic pH. The combination of calcium alginate and carboxymethyl cellulose exhibits sustained drug release during transit time in the gastrointestinal tract before reaching the colon, and higher adhesion to the colonic mucosa, whose degradation is controlled by colonic microflora [30].

Amylose

Amylose is a linear polysaccharide that is not branched from glucopyranose units (D-1, 4-D-glucose) obtained from starch [64]. Amylose is resistant to pancreatic amylase, so it cannot be digested in the small intestine but can be degraded by *Bacteroides*, and *Bifidobacterium* in the colon [65]. Amylose can maintain its structure against amylase enzyme degradation throughout in-vitro test, so drug release can be controlled [66]. Amylose will swell when in contact with water because it has an elasticity degree. The qualitative testing of corn starch for CDDS using scanning electron microscopy (SEM) showed that hydrolysis of starch can swell due to the formation of pores and enzymatic degradation by α -amylase [67].

Arabinoxylan

Arabinoxylan is a hetero-polysaccharide consisting of linear xylose with arabinose substitution and cross-linking with ferulic acid [68]. Arabinoxylan is fermented and degraded by enzymes produced by the colonic microflora, especially by *Bacteroides* and *Bifidobacterium* [39]. These enzymes include β -xylosidase, xylanase, α -arabinofuranosidase, and β -glucosidase [69]. Arabinoxylan can form covalent gels when there is an enzymatic reaction of ferulic acid, which is influenced by changes in pH, temperature, and ionic strength. When insulin and insulin-glutamic acid are mixed with arabinoxylan, there is an increase in gelation time, which may be due to changes in pH and increased viscosity. In addition, arabinoxylan can form covalent cross-linking, which strengthens the gel. This excipient has been widely used for delivering drugs to the colon site. For instance, the successful delivery of the insulin release profile from arabinoxylan-coated microspheres revealed the biphasic release with the initial release of insulin at pH 1.2 followed by gradual drug release at pH 6.8. When microspheres reach the colon, insulin will be released by colonic microbes fermentation [70].

Dextran

Dextran is a polysaccharide with a linear chain consisting of α -1,6-glucopyranose and α -1,3-glucopyranose, which has a molecular weight of approximately 40 kDa [41,71]. Dextran cannot be digested by glycosidase but degraded by dextranase derived from microflora in the colon [72]. Dextran is a polysaccharide that has been developed for CDDS as a prodrug conjugate because it has good water solubility, low toxicity and immunogenicity, and low polydispersity [73]. The drug-dextran conjugate does not release the drug before the colon because of the steric barrier of the polymer matrix preventing enzymatic degradation in the upper gastrointestinal tract. Depolymerization of matrix dextran by endo dextranase, secreted by bacteria in the colon, produces oligomers that reduce steric resistance and break the dextran-drug bond which can lead to the drug release [72]. Succinic acid and glutamic acid are commonly used as a link between drugs and dextrans to increase drug release in the colon [74]. Shrivastava *et al.* [73] have reported the use of dextran in a CDDS tablet [34]. Their study found that the release of 5-ASA-dextran-conjugated observed in rat cecal for 24 hours showed that the percentage

of drug released in the colon was $51.25\% \pm 1.48\%$. The other study also supported that an *in vivo* test in rat cecal of celecoxib-dextran-glutamic acid conjugate showed that 55% of the drug was released at 10 hours and 75% at 24 hours [72].

Guar Gum

Guar gum is a polysaccharide that can be used for CDDS. Guar gum can control drug release due to its hydrophilic properties and is susceptible to microbial degradation in the colon [75]. Guar gum has a linear galactomannan chain consisting of β (1 \rightarrow 4) mannose which is bound to 1 \rightarrow 6 with galactose units [43]. The mechanism of drug release using guar gum is swelling of a polymer matrix which is influenced by the relaxation properties of the matrix and the rate of diffusion of water into the polymer matrix. The mechanism of drug release from the polymer can be divided into three stages. They are the penetration of water molecules from outside the system into the matrix, polymer swelling, drug dissolution in the polymer, and drug diffusion through the swollen matrix [43,76]. One study conducted by Seeli *et al.* found that the release of ibuprofen from beads coated with guar gum succinate-sodium alginate showed that 20% of the drug was released at pH 1.2 within 3 hours and 50% of the drug was released at pH 7.4 after 3 hours. This can be caused by the electrostatic repulsion of the negatively charged guar gum succinate-sodium alginate group in a buffer solution of pH 7.4 [75]. The 5-ASA was fabricated using guar gum and then evaluated for the percentage of 5-ASA release. The result showed a higher 5-ASA release in the media of pH 6.8 and 7.4 than that in the media of pH 1.2. This can be caused by the hydrophilic group being protonated at pH 1.2 to prevent the interaction between water and the polymer system, while at alkaline pH, the hydrophilic group will form hydrogen bonds with water to allow water penetration. When water penetrates the polymer system, the polymer will swell, and the drug in the matrix diffuses out [43].

Inulin

Inulin is a fructant consisting of oligomers and polymer mixtures that have 2 to 60 β (2-1) D-fructose monomers linked to the α (2-1) D-glucose group [45]. Inulin can be used as an excipient for colonic targeted drug release because it protects against degraded drugs in the stomach and small intestine. The stomach and small intestine have no inulinase that can degrade inulin. Inulin is only significantly hydrolyzed by inulinase produced by *Bifidobacterium* in the colon and not by digestive enzymes in the upper gastrointestinal tract [77]. When it reaches the colon, inulin can be degraded in the presence of the inulinase [78]. The swelling test showed that the addition of 30% inulin to the formulation significantly increased matrix polymer development compared to the one formulated with polymethacrylate only. This can be due to the inulinase in the medium, which diffuses into the polymer chain, hydrolyzing the inulin fructose, thereby increasing polymer swelling [79]. *In vitro* drug release of ibuprofen-coated inulin and Shellac showed that using Shellac as an outer enteric coating could prevent premature drug release in acidic media [78]. Another study by Akhgari *et al.* found that *In vitro* degradation of inulin hydrogel using inulinase showed that inulinase could degrade

inulin in the colon and functioned well at pH 5.0 in sodium acetate buffer [79].

Carrageenan

Carrageenan is an anionic polysaccharide containing sulfate, D-galactose, and 3,6-anhydrogalactose units connected by α -1,3 and β -1,4 glycosidic bonds. There are 3 main types of carrageenan based on its bonds, such as λ -carrageenan with three sulfate groups repeating unit of disaccharide; κ -carrageenan which has one sulfate group and ι -carrageenan that has two sulfate groups [46]. Kappa-carrageenan is a type of carrageenan that has the highest gelling strength compared to other types of carrageenan [80]. The mechanism of drug release by kappa-carrageenan is swelling which is influenced by pH conditions. At pH 1.2, the kappa-carrageenan swelling ratio was higher than pH 6.8 due to electrostatic repulsion between sulfate anions through deprotonation of $-\text{SO}_3\text{H}$ groups with pKa of 4.9. When the pH is increased, the K^+ cation charge interferes with the electrostatic repulsion between the sulfate anions thereby reducing the swelling rate [47]. A high concentration of kappa-carrageenan will increase its swelling ratio [81]. A study of carrageenan conducted by Leong *et al.* revealed that the release study of Fluorescein isothiocyanate-labeled dextran (FD-4) coated carboxymethylated kappa-Carrageenan beads showed that $23\% \pm 2\%$ and $90\% \pm 3\%$ of FD-4 was released in simulated gastric and colonic fluid, respectively [80]. In another study, the release of tramadol coated with UiO-66 and kappa-carrageenan showed the lowest drug release at pH 1.2 and the highest drug release at pH 7.4 or colon condition [47].

Chitosan

Chitosan is an amino polysaccharide consisting of β -D-glucosamine and N-acetyl-D-glucosamine repeating units linked by $1 \rightarrow 4$ glycosidic bonds [82]. Chitosan is included in the polycation type polymer because it has an ionizable amine group [83]. The mechanism for drug release from chitosan is swelling, which depends on pH conditions. The higher polymer concentration and stronger hydrogen bonds may inhibit the penetration of the acid solution into the matrix. The $-\text{COOH}$ groups of the polymer are not ionized in the acidic solution and this induced electrostatic repulsion. It is inversely proportional to the condition of pH 7.4, where the swelling index increases with increasing polymer concentration. The presence of carboxyl groups in ionized form induces electrostatic repulsion at base condition [84]. Another mechanism of drug release is mucoadhesive properties. The amine groups that have a positive charge on chitosan will interact with mucin ions (sulfonic acid and sialic acid residues), which are negatively charged [85]. The release study of tetrandine beads coated with chitosan tripolyphosphate showed that 5.45% and 1.72% of tetrandine release at pH 1.2 when combined with 10% hydroxypropyl methylcellulose phthalate (HPMCP) and chitosan 10% CAP, respectively. The increase in drug release occurred significantly at pH 6.8 media in 315 minutes caused by the polymer layer being eroded so that the matrix could be hydrated and swollen [86]. Another research presented the release study of curcumin coated with chitosan which showed low release at pH 1.2 media (approximately 5.6%)

and increased at pH 6.8 to 7.2 (approximately 10.8%). This could be due to the presence of cross-links which strengthen the integrity in acidic conditions [87].

Chondroitin sulfate

Chondroitin sulfate is a negatively charged polysaccharide that has a sulfate group consisting of repeating disaccharide units of β -1,3 N-acetyl galactosamine and β -1,4 D-glucuronic acid [88]. Chondroitin sulfate is a water-soluble polysaccharide and can be degraded by *B. thetaiotaomicron* and *B. ovatus* in the colon [50]. The drug delivery mechanism of chondroitin sulfate is by gelling and swelling. The percentage of the swelling index will increase when the chondroitin sulfate concentration is increased. Chondroitin sulfate has sulfonate ($-\text{SO}_3^-$), hydroxyl ($-\text{OH}$), and carboxylate ($-\text{COO}^-$) groups at higher pH (7.4) undergo ionization or deprotonation to become negatively charged that produce electrostatic repulsion which increases the swelling ratio [51]. Ramasamy *et al.* [88] conducted a release study of aceclofenac coated with chondroitin sulfate and enteric polymer [Eudragit S-100 and L-100] which showed that 10% of the drug was released in medium pH 1.2 for 2 hours and increased at pH 7.4 added with an enzyme to $102, 34\% \pm 0.36\%$ for 8 hours. This is due to the continuous swelling to form a viscoelastic matrix so that the drug can be released [50]. Similarly, another study showed that the release of oxaliplatin from the chondroitin sulfate-acrylic acid hydrogel depended on the pH, namely 19% at pH 1.2 and 94% at pH 7.4 for 36 hours [51].

Lactulose

Lactulose is a disaccharide obtained from isomerization of lactose which consists of fructose and galactose. Lactulose cannot be digested in the upper gastrointestinal tract but can be degraded by *Lactobacillus* and *Bifidobacterium* in the colon [89,90]. Lactulose is used in the Novel Colon Targeted Delivery System (CODES™) formulation to induce specific drug release in the colon by combining pH-dependent release mechanisms and the enzymatic activity of the colonic microflora [91]. CODES™ consists of a tablet core, an acid-soluble polymer (Eudragit® E100), and an enteric polymer (Eudragit® L100). When the drug reaches the colon, lactulose will be converted into lactic and short-chain organic acids through β -galactosidase secreted by microflora in the colon. The presence of this organic acid can decrease the pH so that it can dissolve the acid-soluble polymer and the drug can be released [53,92]. The release of CODES-based budesonide with a concentration of 50% lactulose, 30% Eudragit E and 12% Eudragit FS30D can reach 82.5% on a pH 6.8 medium containing rat cecal [54]. In addition, the release of etoricoxib from CODES demonstrated that drug release in pH 1.2 medium ranged from 0.1%–0.5% and pH 6.8 medium with *Lactobacillus sporogenes* ranged from $63.671 \pm 1.62\%$ to $98.929 \pm 1.69\%$ [53].

Locust bean gum

Locust bean gum is a linear polysaccharide consisting of β -(1,4)-D-mannose units and each fourth or fifth mannose unit is replaced by a 1,6 α -galactose side chain. Locust bean gum is degraded by enzymatic activity in the colon. These enzymes are

β -mannanase, β -mannosidase, and α -galactosidase secreted by *Bacteroides* and *Ruminococci* [93]. Locust bean gum swelling tests show that it can absorb up to 130% water after 7 hours of hydration. When the polymer is in contact with water, water will penetrate and reach the core of the tablet, which makes the polymer swell so that it can control drug diffusion [94]. Ibuprofen coated with locust bean gum was not released at pH 1.2 or 7.4 but it can release $94.46\% \pm 0.92\%$ after 26 hours at pH 6.8 [55]. Similarly, the release study of 5-FU coated with locust bean gum and HPMC stated that the drug release ranged from 2.59% to 7.52% for 5 hours at pH 1.2 and 85.94% to 99.51% at pH 6.8 with 4% rat cecal [95]. Furthermore, the drug release of mesalamine coated with locust bean gum-Eudragit S100 proved that 0% of the drug was released at pH 1.2, and the drug release increased when pH increased. The highest percentage of

cumulative drug release for 24 hours can reach 96.73% in colon conditions [96].

Pectin

Pectin is a polygalacturonic acid that has a negative charge at neutral pH with a pKa value of 3.5 [97]. Low pectin concentrations will produce rapid degradation of pectin and premature release of the drug. By increasing the concentration of pectin, a stiff gel that cannot be degraded by enzymes will be formed and this can reduce the rate of drug release [57]. The use of enteric polymers and cross-linking agents can be employed for obtaining delayed release of drugs and increasing drug release in the colon [98]. The initial release of the drug can be prevented by using a combination of pectin and ethyl cellulose with a ratio of 1:2. The 5-FU released $4.1\% \pm 0.4\%$ in the first 5 hours in the simulated stomach and intestines media,

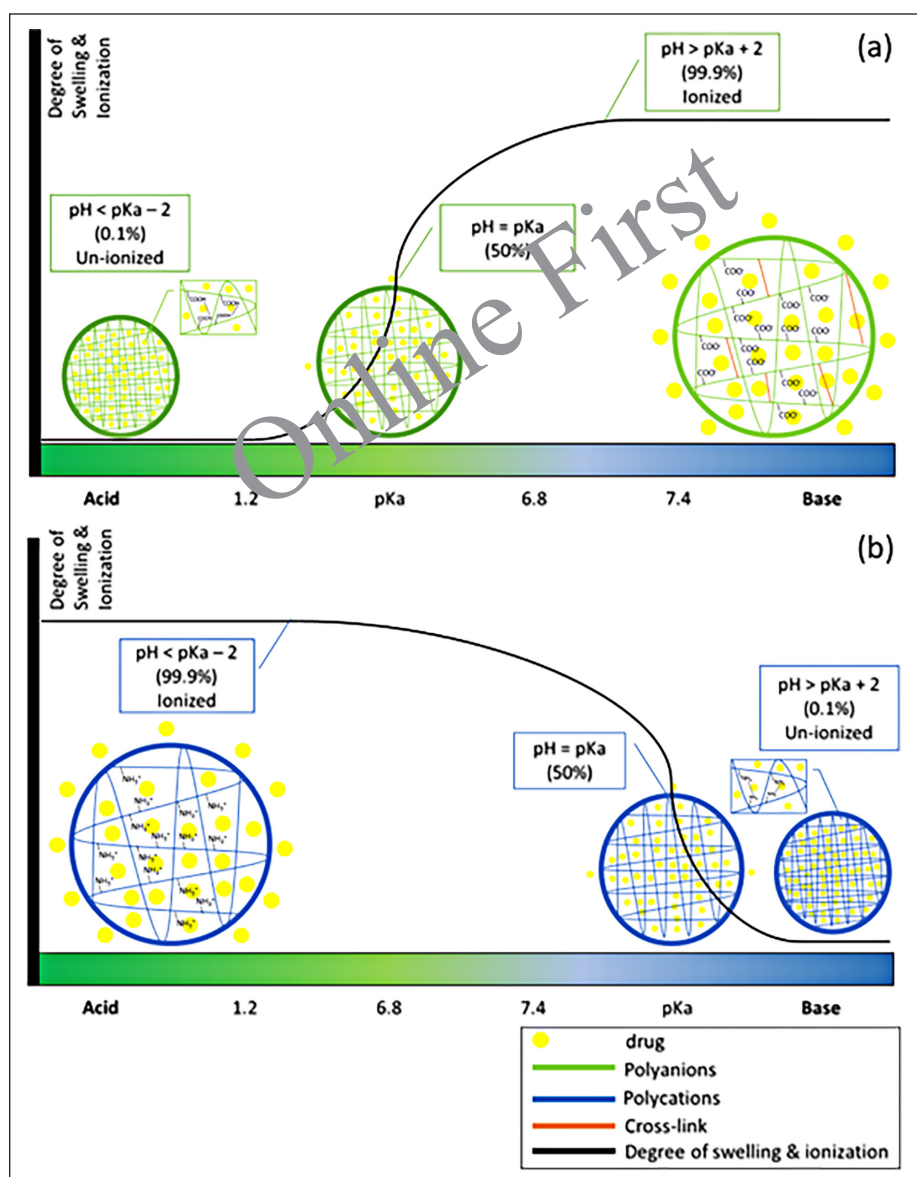


Figure 1. Relationship of pH, swelling, and ionization of polymer matrix of (a) polyanions and (b) polycations.

while in the simulated colon media with the added rat cecal can release $85.0\% \pm 0.3\%$ drug for 24 hours [99]. Another pectin-drug delivery mechanism is the prodrug system. The presence of enzymatic degradation by bacteria in the colon causes drug release from its conjugate bonds. The prodrug of metronidazole with pectin released 1% to 5% of the drug in medium pH 1.2 for 2 hours and pH 6.8 for 6 hours and increased at pH 7.0 with rat cecal content of 67.9% for 8 hours. This strongly indicates that the presence of enzymatic degradation by bacteria in the colon causes the release of drugs from their conjugate bonds [100].

Cyclodextrins

Cyclodextrins are α -1,4-linked cyclic oligosaccharides consisting of several glucopyranose units [101]. The targeted colonic drug delivery system approach using β -cyclodextrins is through the formation of drug conjugates with β -cyclodextrins. These conjugates will form esters or amide bonds from drug carboxyl groups and hydroxyl groups on β -cyclodextrins to improve chemical and physical stability, solubility, and biocompatibility. Degradation of β -cyclodextrins in the colon is due to hydrolysis by α -amylase, an enzyme secreted by *Bacteroides*, into saccharide conjugates, such as maltose and ester conjugates. The ester conjugate is then hydrolyzed by the carboxyl-esterase so that the drug can be released [59]. Madan *et al.* [102] demonstrated that the dissolution test of the cyclodextrin-bromonoscipine complex coated with guar gum at pH 7.4 showed that only 7.9% of the drug was released. Meanwhile, at pH 6.8, the cyclodextrin-bromonoscipine complex coated with guar gum showed that 30.4% of the drug was released. In simulated colonic media with a pH of 7.0 and a content of 6% rat cecal, 55.6% of the drug was released. Drug release can be prolonged because of the cross-links between glutaraldehyde and the hydroxyl group of galactose and mannose thereby preventing water absorption. When it reaches the colon, drug release is induced by enzymatic reactions by colonic bacteria. Another study by Arulraj *et al.* [60] confirmed that the release study of celecoxib-coated guar gum-cyclodextrin matrix showed 1.6%, 7.2%, and 88.4% of the drug was released at pH 1.2 for 2 hours, pH 7.4 for 6 hours and pH 6.8 for 2 hours, respectively.

Polymer

Polymers can be classified according to their constituent units as homopolymers consisting of one type of repeating unit and copolymers consisting of two or more types of repeating units. Copolymers can be classified according to the arrangement of the units as alternating, random, block, or graft. Polymers are widely used in the formulation of targeted delivery systems to the colon because of their ability to dissolve, swell, and change their conformation due to protonation or deprotonation caused by pH changes in the gastrointestinal tract. Polymers can also be classified into two types based on their ionization properties, namely polyanions and polycations, illustrated in Figure 1 [83]. Polyanions have ionizable acid groups, such as carboxylic acid ($-\text{COOH}$), sulfonic acid ($-\text{SO}_3\text{H}$), or phosphonic acid ($-\text{PO}_3\text{H}_2$), which bind to the polymer. When there is an excess of protons in acidic pH, the acid group will experience protonation to form polymer bonds.

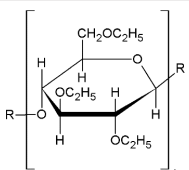
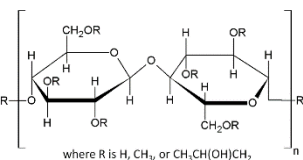
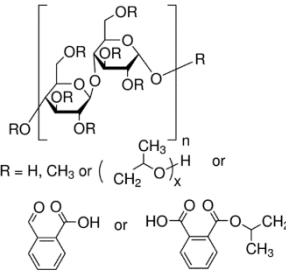
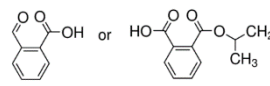
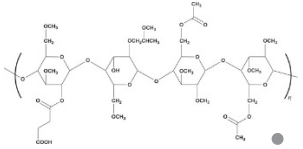
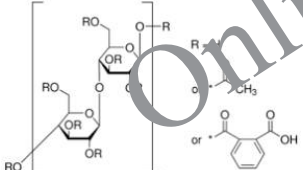
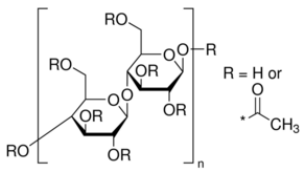
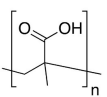
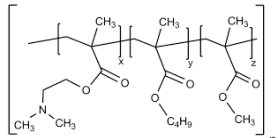
Conversely, the acidic groups will be ionized in an alkaline pH and release protons, causing the development of the polymer due to electrostatic repulsion from negatively charged groups [83]. The carboxylic group will accept protons at low or acidic pH and release protons at high pH values [103]. The release of the drug from the system occurs when polymers swell due to pH and ion exchange [104]. The polycation has an ionizable base group, such as an amine ($-\text{NH}_2$), which binds to the polymer. Polycation will accept protons in an acidic pH environment, resulting in a positive charge, which leads to the swelling of the polymer system due to the electrostatic repulsion. Some examples of synthetic polycation are polyvinyl amine, poly(2-aminoethyl methacrylate), and polyethylene imine (PEI). One example of natural polycation is chitosan. Excipients of polymer used for colon-targeted drug delivery system can be seen in Table 2.

Cellulose derivatives

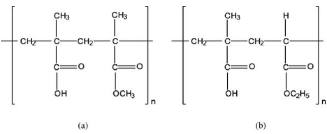
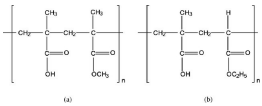
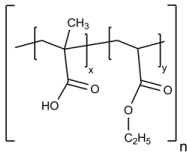
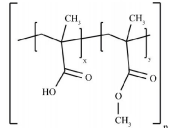
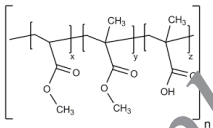
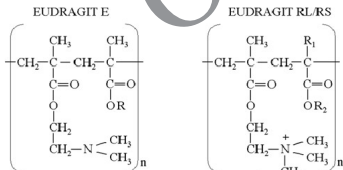
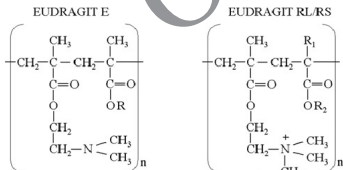
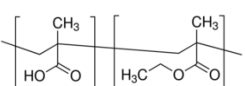
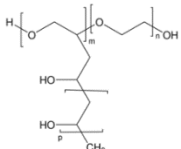
The cellulose group polymers that are often used for CDDS are ethyl cellulose, hydroxypropyl methylcellulose (HPMC) and their derivatives, and cellulose acetate derivatives. Ethyl cellulose is a linear polysaccharide with a hydrophobic β -anhydroglucose ring which has a hydroxyl group that is substituted with an ethoxy group [105]. Ethyl cellulose is often used as a polymer for the sustained release of drugs. The combination of enteric polymer (Kollicoat MAE 100DP) and ethyl cellulose as a binder can protect the release of the drug in an acidic medium for 2 hours. When it reaches a pH of 6.8, the enteric polymer will dissolve first and ethyl cellulose, which dissolves only at a lower pH, can be used to protect the drug released in the small intestine [106]. In terms of HPMC, it is a hydrophilic polymer that can be utilized for sustained release systems with gel formation [56] so that the drug release can be prolonged [107,108]. Increasing the HPMC concentration can reduce drug release because this polymer tends to form a gel at high concentrations, thereby reducing drug diffusion [37]. One of the modified HPMCs is hydroxypropyl methylcellulose phthalate (HPMCP). It is an enteric polymer consisting of phthalate esters linked to HPMC. Curcumin pellets coated with Pectin and HPMC (1:3) showed a minimum release at pH 1.2 of 0.19%, pH 7.2 of 19.72%, and pH 6.8 of 89.91% during 2 hours [108]. In addition, flurbiprofen loaded in an HPMC matrix and coated with Eudragit S showed a release of $18.41\% \pm 0.68\%$ after 5 hours in simulated gastric and small intestine medium and increased to $100.43\% \pm 3.33\%$ in colonic simulation media after 24 hours [107].

HPMCP is often used as an enteric polymer to prevent drug release in the stomach [109]. Another polymer that is widely used for preventing drug release in acidic environments is hydroxypropyl methylcellulose acetate succinate (HPMCAS). The addition of acetyl and succinyl groups to HPMC makes this polymer undissolvable at low/acidic pH. The release of metoprolol succinate coated with the combination of Eudragit-P4135F and HPMC-AS nanoparticles showed that 0% drug was released at pH 1.2 and 94.34% at pH 6.8 [110]. Another study also supported that the release of mesalazine coated with HPMCAS showed that $0.98\% \pm 1.28\%$, $6.451\% \pm 2.14\%$, and $98.47\% \pm 1.34\%$ of the drug was released at pH 1.2 for 2 hours,

Table 2. Excipients of polymer used for CDDS.

Excipient	Structure	Optimum pH	CDDS mechanism	Reference
Ethyl cellulose		-	Binder, Sustained release	[105,106]
Hydroxypropylmethyl cellulose (HPMC)	 where R is H, CH ₃ , or CH ₂ CH(OH)CH ₂	-	Time-dependent	[116,117]
HPMC phthalate (HPMC-P)	 R = H, CH ₃ or $\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2 - \text{O} \end{array} \right)_x$ or 	4.5 - 4.8	pH-dependent	[112]
HPMC acetate succinate (HPMC-AS)		> 6.0	pH-dependent	[111,118]
CAP		6.0	pH-dependent, swelling	[115,119]
CAT		5.5	pH-dependent	[120]
Polyacrylic acid (PAA)	$\left(\text{---CH}_2\text{---CH---} \right)_n$ COOH	5 - 6	Polyanion, pH-dependent, swelling	[121,122]
Polymethacrylic acid (PMAA)		4 - 5	Polyanion, pH-dependent, swelling	[121,122]
Eudragit E100		5.0	Polycation, prevents the release of the drug in the small intestine, the release in the colon in the presence of acids	[91,124]

(Continued)

Excipient	Structure	Optimum pH	CDDS mechanism	Reference
Eudragit L100	 <p>(a) (b)</p>	6.0	Polyanion, pH-dependent, swelling	[125,126]
Eudragit L100-55	 <p>(a) (b)</p>	5.5	Polyanion, pH-dependent, swelling	[127]
Eudragit L30D-55	 <p>(x) (y)</p>	5.6	Polyanion, pH-dependent, swelling	[127]
Eudragit S100	 <p>(x) (y)</p>	7.0	Polyanion, pH-dependent, swelling	[125,126]
Eudragit FS30D	 <p>(x) (y) (z)</p>	8	Polyanion, pH-dependent, swelling	[128]
Eudragit RL100	<p>EUDRAGIT E</p>  <p>EUDRAGIT RLRS</p> <p>R = CH₃, C₂H₅</p> <p>R₁ = H, CH₃ R₂ = CH₃, C₂H₅</p>	-	Polycation, Time-dependent	[129,130]
Eudragit RS100	 <p>R = CH₃, C₂H₅</p> <p>R₁ = H, CH₃ R₂ = CH₃, C₂H₅</p>	-	Polycation, Time-dependent	[128,129]
Kollocoat MAE 100P	 <p>(n) (m)</p>	5.5	pH-dependent	[131]
Kollocoat IR	 <p>(m) (p)</p>	-	Binder, colonic solubility enhancer	[132]

(Continued)

Excipient	Structure	Optimum pH	CDDS mechanism	Reference
Kollocoat Smartseal 30D	<p>$m = 7; n = 3$</p>	-	time-dependent, sustained release	[133]
Poly(lactic acid-co-polyglycolic acid) (PLGA)		-	Polymer biodegradable, erosion, sustained release	[134,135]
Shellac		6,9 – 7,5	pH-dependent, swelling	[136,137]

pH 6.0 for 3 hours and pH 7.2 for 5.5 hours, respectively [111]. Additionally, the release of metronidazole coated with Eudragit and Chitosan-HPMCP showed a minimum release at pH 1.2 of $5.57\% \pm 1.34\%$ and $8.46\% \pm 2.49\%$ in 2 hours and 5 hours, respectively. The release of metronidazole increased in colon simulation media due to degradation by colonic microbes [112].

CAP is another enteric polymer that dissolves at a pH above 6.0 [113]. CAP is a cellulose derivative that has a hydroxyl group which is acetylated and esterified with phthalic acid [114]. The *in vitro* study of the release of tetracycline tromethamine capsules coated with guar gum and CAP showed no drug release in the first 2 hours in a pH 1.2 medium and 21.29% of the drug released at pH 7.4 for 3 hours. Meanwhile, the cumulative release can reach 99.18% for 25 hours in colonic conditions at pH 6.8 [115]. Different from CAP, cellulose acetate trimelitate (CAT) is an enteric polymer derived from cellulose which in the hydroxyl group undergoes acetylation and esterification with melicic acid [114]. Microspheres containing indomethacin coated with CAT experienced a 10–15% release in the first 30 minutes. This release can occur due to incomplete entrapment of indomethacin in the microsphere. At a pH of 6.8, there was an increase in drug release, and it reached 100% in one hour. This is due to the increasing solubility of CAT at pH 6.8 where CAT has an optimum solubility above pH 5.5 [120]. These enteric polymers are frequently used in combination with other polymers, such as polysaccharides, to increase the effectiveness of colonic delivery [111].

Poly(acrylic acid) (PAA) and poly (methacrylic acid) (PMAA)

PAA is an acrylic acid polymer that has a carboxylic group in each monomer unit or every two carbon atoms of the main chain [138]. This polymer contains free carboxylic acid which functions as a pH-sensitive delivery system. These carboxylic groups do not ionize at acidic pH and ionize at neutral or weak alkaline pH [139]. In acidic pH, the polymer will form hydrogen bonds in the carboxylic group, thus releasing the

drug from the polymer matrix. On the other hand, at pH 7.6 (above the pKa of PAA), the carboxyl group will be ionized to form COO⁻ which is negatively charged, causing electrostatic repulsion. This results in the polymer swelling and the drug can diffuse out of the matrix. The release study of doxorubicin without using PAA showed 78% and 10% at pH 2.0 and 7.6. However, the release of doxorubicin coated with PAA showed 20% and 64% drug release at pH 2.0 and 7.6 for 12 hours, respectively [121].

Poly (methacrylic acid) (PMAA) or poly (2-methyl-2-propenoic acid) is a polymer of methacrylic acid having a methyl group substituted at carbon position 2 [140]. PMAA has a pKa value ranging from 4 to 5, so PMAA can maintain its structure at gastric pH and will swell at neutral pH due to the ionization of carboxylic groups and electrostatic repulsion [123]. The release of ibuprofen-coated GGOg-PMAC hydrogel showed that the drug could be released for 12%, 38%, and 50% at pH 1.2 for 3 hours, pH 7.4 for 4 hours and pH 6.8 for 21 hours, respectively [141].

Eudragit[®]

Eudragit[®] is a pH-dependent copolymer of methacrylic acid which is a registered trademark of Rohm Pharmaceuticals, Darmstadt, Germany [142]. Eudragit[®] E is a cationic polymer that dissolves at an acidic pH of about 5.0 and is used to prevent drug release in the small intestine. The lag time of capsules coated with Eudragit E-100 increased when the pH of the system also increased. The solubility of Eudragit[®] E-100 increases in the pH below 6.5. Eudragit[®] E-100 can prevent drug release as they are not dissolved at neutral pH in the small intestine [124].

On the other hand, Eudragit[®] L and Eudragit[®] S are polyanion polymers that can be used to prevent drug release in the stomach and dissolve at the pH of the intestine. Eudragit[®] L is a copolymer of methacrylic acid and methyl methacrylate with a ratio of 1: 1 having a solubility at pH 5.5 to 6 whereas

Eudragit® S is a combination polymer of methacrylic acid and methyl methacrylate (1:2), has a solubility at pH 6.5 [139]. Metronidazole-coated chitosan microspheres release study with Eudragit L-100 showed 1.4% ± 0.04% released at pH 1.2 for 3 hours. Eudragit L-100 dissolves at pH above 6.0 so that at pH 6.8 it is 6.7% ± 0.25% for 4 hours. The drug release after 12 hours on Eudragit L-100 was 69.3% ± 3.12%. The addition of rat cecal content increased drug release to 82.4% ± 3.28%. The study of metronidazole release in chitosan microspheres coated with Eudragit S-100 showed that there was no drug release at pH 1.2 during the first 3 hours. Meanwhile, at pH 6.8, it showed 56.9% ± 2.65% for 12 hours. The addition of rat cecal contents increased drug release to 69.8% ± 3.17% [125]. Similarly, the release of aceclofenac from a chitosan matrix coated with Eudragit L-100 and S-100 showed no drug release at pH 1.2 and 9.2% ± 0.62% of the drug released at pH 7.4. The condition of pH 7.4 added with rat cecal contents showed drug release of 102.24% ± 1.2% due to the presence of enzymes that penetrate the gel layer which can lead to gel erosion and increased drug release [126].

Eudragit® RS and Eudragit® RL are the other types of polymer that can be used for CDDS. Drug release from Eudragit® RL and Eudragit® RS is time-dependent or sustained release. Eudragit® RS and Eudragit® RL are copolymers of acrylic and methacrylic acid esters, each containing a quaternary ammonium group between 4.5% and 6.8% (Eudragit RS), and 8.8% and 12% (Eudragit RL) [127]. The release study of Capecitabine microspheres indicated that 6.79% ± 1.85% to 3.59% ± 1.23%, 7.07% ± 1.23% to 3.22% ± 1.56%, and 3.86% ± 0.74% to 2.99% ± 0.82% at pH 1.2 in the first 4 hours when coated with Eudragit RL-100, Eudragit RS-100, and Eudragit RL/RS-100, respectively. The cumulative drug percentage at pH 6.8 of 96.80%–79.17% for Eudragit RL-100, 94.49%–71.82% for Eudragit RS-100, and 97.07%–83.66% for Eudragit RL/RS-100 [129]. Based on the different properties of Eudragit®, EUDRACON is a combination system for CDDS depending on pH and time by combining Eudragit® RL or Eudragit® RS (depending on time) with Eudragit® FS30D (depending on pH) [143].

Kollocoat®

Kollocoat® is an excipient produced by BASF, Germany. Several types of Kollocoat® that can be used for CDDS are Kollocoat® IR, Smartseal 30D, and MAE 100P. Kollocoat® IR is a copolymer of polyvinyl alcohol and polyethylene glycol. The addition of Kollocoat® IR to the formulation aims to increase the rate of drug dissolution in the colon. The prednisolone coated with Kollocoat IR and Eudragit S-100 release study showed no release at pH 1.2 for the first 5 hours and then a sharp increase in pH 7.4 at 6 hours [132].

Different from Kollocoat® IR, Kollocoat® Smartseal 30D is a copolymer dispersion of methyl methacrylate and diethylaminoethyl methacrylate with a ratio of 6:4. The uses of Kollocoat® Smartseal 30D showed an increase in the drug released after 3 hours. This suggests that increasing Kollocoat® Smartseal 30D will increase the delay time and inhibit drug diffusion. The release study of the combination of chitosan and Kollocoat Smartseal 30D (25:75) indicated that drug release of 0.1% ± 0.04% at pH 1.2 in 2 hours, 9.1% ± 0.7% of drug

released after 310 ± 6.0 minutes and in colon simulation liquid with the addition of microflora there was a sharp increase at 562 minutes [133].

Kollocoat® MAE 100P is a copolymer of methacrylic acid and ethyl acrylate with a ratio of 1:1 [144]. Kollocoat® MAE 100P showed that enteric polymers could protect against drug release at pH 1.2. Kollocoat® MAE 100 P has optimal solubility at pH above 5.5. Kollocoat MAE 100P begins to dissolve at pH 4.6 and releases 10% of prednisolone. Moreover, the drug release of prednisolone can reach 80% at pH 6.8 and 10% of the residual drug at pH 7.4 [131].

Poly (lactic-co-glycolic acid) (PLGA)

PLGA is a linear aliphatic copolymer consisting of lactic acid and glycolic acid monomers linked by ester bonds. PLGA can be used for drug delivery systems and drug encapsulation for controlled release. PLGA can be degraded by the hydrolysis of ester groups [145]. The combination of 5 mg Ibuprofen nanoparticles and 95 mg PLGA showed a time-dependent release [134]. PLGA can be used as a nanoparticle polymer because it is biodegradable and biocompatible. The release of the drug from the PLGA polymer was caused by erosion and degradation [139]. An *in vitro* release study of budesonide nanoparticles coated with PLGA at pH 6.8 for 72 hours showed a burst release of 52% in the first 1 hour followed by a final release of 58% in 72 hours. The burst effect may be due to the presence of drug molecules not encapsulated in the polymer core or drugs on the surface so that they can be released quickly [146]. The release study of curcumin by PLGA showed that 10% of the drug was released at 1,2 and 6,8 in 5 hours. The release increased by 56%, and 78% in the first 24 and 48 hours at pH 7.4, respectively. This is also influenced by the higher solubility of curcumin at neutral pH than under acidic conditions [147].

Shellac

Shellac is a resin secreted by the insect *Laccifer lacca* that prevents drug release in the upper gastrointestinal tract [148]. Shellac is a biodegradable hydrophobic polymer with a pKa of 5.6 to 6.6 so Shellac does not dissolve in gastric pH [136]. However, it is unsurprising that this type of polymer will dissolve in neutral pH [149]. The release study of anthocyanin-pectin beads coated with 15% Shellac showed 46%, 46%, and 88% of the drug released at pH 2.0, pH 6.3, and pH 6.2 with the addition of enzymes, respectively. This result strongly indicates that increasing the Shellac concentration will decrease the rate of drug release [150].

MECHANISM OF EXCIPIENTS IN COLON DRUG DELIVERY SYSTEM

The various mechanisms of excipients in CDDS can be described in Figure 2.

pH-dependent system

This pH-dependent delivery system uses an approach to pH differences in the gastrointestinal tract. The pH-dependent drug delivery systems are essential for targeted

drug release in the colon because they utilize the distinct pH variations throughout the gastrointestinal tract to deliver the drug only to the colon site. In the stomach, under normal conditions, the pH is between 1 and 3.5 and can increase to 4.6 after eating. Meanwhile, the pH of the small intestine ranges from 5.5 to 7.5, and in the colon, it is around 5.7 to 6.7 [151]. The pH conditions in the colon are slightly lower compared to the small intestine due to acidification of the colonic contents due to fermentation products from bacteria in the colon [152,153]. Based on the differences in physiological pH conditions of the gastrointestinal tract, excipients that are insoluble at acidic pH can be used to protect the drug from being released at the gastric site but can dissolve at alkaline pH when the drug reaches the intestine and colon [153]. The excipient used has special characteristics, namely that it does not dissolve under acidic conditions, but the dissolution rate of the excipient will increase when the pH shifts towards alkaline conditions [154]. Excipients that can protect drugs from acidic pH are enteric polymers or polyanions. Examples of enteric

polymers include HPMC phthalate (HPMC-P), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), CAP, cellulose acetate trimeliat (CAT), PAA, Poly methacrylate, Eudragit L, Eudragit S, Eudragit FS30D, Kollicoat MAE 100P, and Shellac. Enteric polymers play a crucial role in pH-dependent drug delivery systems by preventing drug release in the acidic environment of the stomach. These polymers are designed to remain insoluble at low pH values, thereby protecting the drug from early release. The enteric polymers will dissolve in the more alkaline conditions of the colon, which can allow the drug to be released.

The mechanism of drug release from this matrix is based on the pKa of the polymer and the pH of the medium or system. In general, using polyanion polymers is an ideal excipient to prevent drug release at lower pH values and promote the release of higher pH drugs [83]. Based on the Henderson-Hasselbalch equation (Equation 1), the polymer will be fully ionized at a pH above $pK_a + 2$ and almost not ionized at a pH below $pK_a - 2$. Meanwhile, when the pH of the system is the

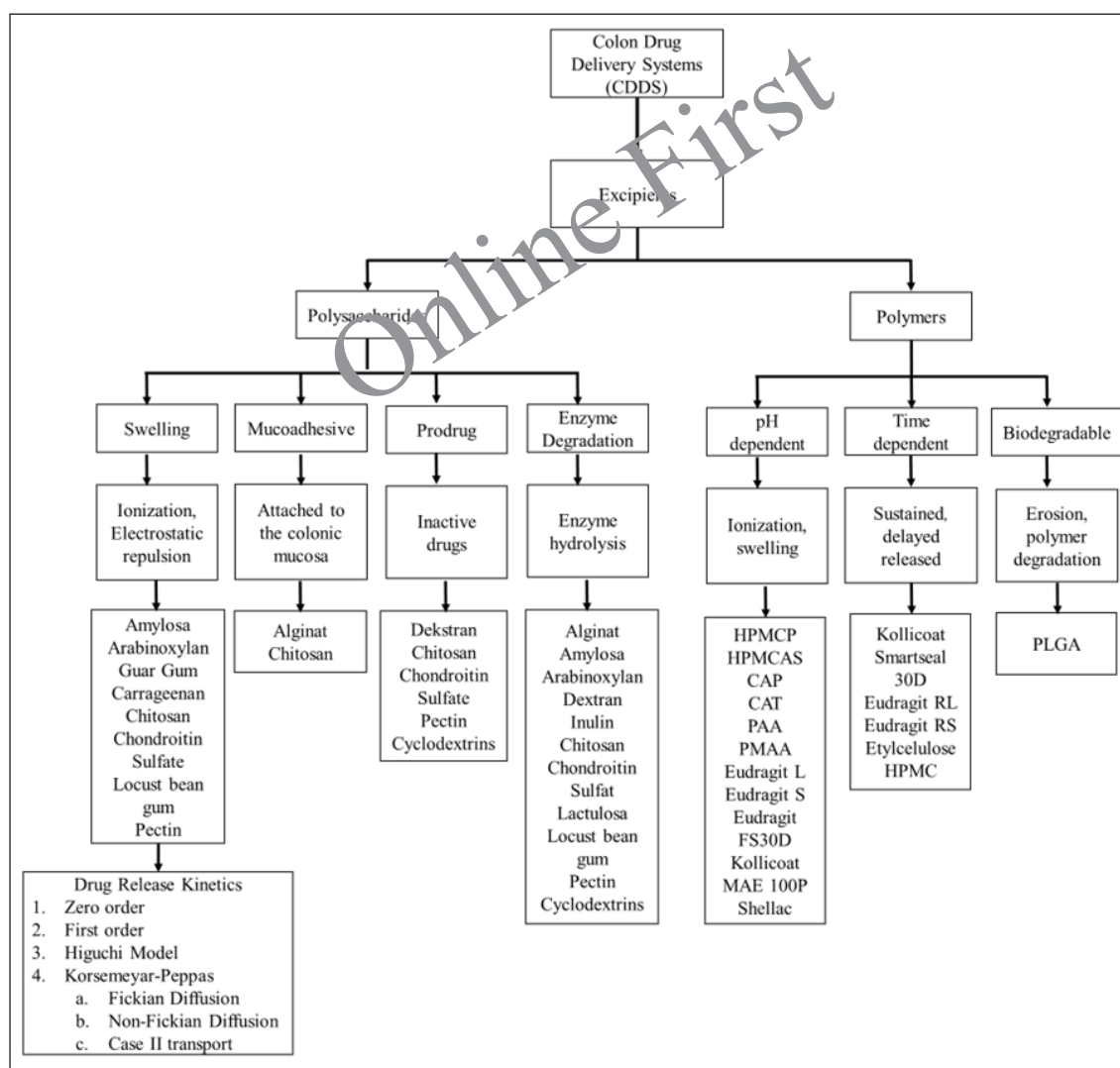


Figure 2. Various mechanisms of excipients for CDSS.

same as the pKa of the polymer, the ionization value is 50% [20].

$$\text{pH} = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{HA}]} \quad (\text{Equation 1})$$

where pH is the pH value of the solution, pKa is the acid-ionization constant of the polymer, $[\text{A}^-]$ is the concentration of the conjugate base or the ionized form of the polymer, and $[\text{HA}]$ is the concentration of the weak acid or the non-ionized form of the polymer. This ionization behavior affects the polymer's solubility and swelling properties, which in turn influences drug release. For instance, a polymer that is non-ionized and less soluble at acidic pH will protect the drug from release in the stomach but will dissolve and release the drug in the alkaline environment of the colon.

Figure 1 shows the drug-released mechanism of polymers, both polyanion and polycation, in several pH conditions [83]. The pH-dependent system can be affected by the swelling properties of polymers. The swelling ratio is the ability of the polymer to expand when hydrated so that it can trigger the release of drugs that are in the matrix. The swelling ratio is influenced by the presence of acid group ionization, hydrogen bonds, cross-linking of polymers, and the concentration of coatings with other polymers. In polyanions, acidic groups such as carboxylic (COO^-) will undergo protonation to become COOH under acidic conditions. This protonation forms hydrogen bonds which prevent the polymer from swelling. Conversely, at alkaline pH, the carboxyl group will be deprotonated or lose protons so that it ionizes and becomes negatively charged (COO^-). The presence of this negatively charged group causes electrostatic repulsion of similar ionic charges which can lead to polymer swelling and trigger the release of the drug from the polymer matrix [83].

Time dependent

The time-dependent targeted delivery system to the colon uses a non-biodegradable polymer that can coat the drug core where the excipient can be dissolved during the drug transit to the colon so that the new drug core is released at the colonic site. This system relies on the transit time of the drug from the gastrointestinal tract where the drug is expected to be released when the drug reaches the colon [20]. Transit time is crucial for drug release in time-dependent targeted delivery systems because it affects how long the drug remains in the gastrointestinal tract before reaching its intended site of action, such as the colon. The time-dependent system ensures that the drug is released only after a specific period, which aligns with the average transit time to the colon. By adjusting the release mechanism to match these transit times, the system can precisely time drug release in the colon.

The average transit time for the drug to reach the ileocecal junction is 3 to 4 hours and will slow down when it reaches the large intestine, which is around 20 to 35 hours. Increasing residence time in the colon will increase the contact time of the preparation with the microflora in the colon so that this delivery system can be an approach to deliver drugs to the colon [155,156]. Examples of excipients that have a time-

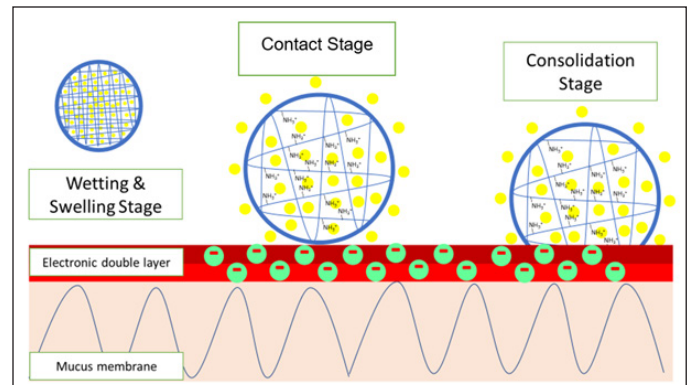


Figure 3. Mucoadhesive properties mechanism using chitosan (polycation).

dependent delivery mechanism include Kollicoat Smartseal 30D, Eudragit RL, Eudragit RS, Ethyl Cellulose, and Hydroxypropyl Methylcellulose. This system can be combined with enteric coating to prevent premature drug release in the stomach [4]. Enteric coatings protect the drug from being released in the acidic environment of the stomach and upper gastrointestinal tract. This ensures that the drug remains intact until it reaches the more alkaline environment of the small intestine and colon. Once the enteric coating is dissolved in the intestine, the time-dependent polymer mechanism takes over. This polymer coating then dissolves according to a set time frame, allowing the drug to be released specifically when it reaches the colon and preventing premature release in the small intestine.

Mucoadhesive system

Mucoadhesive is the property of the drug to be able to attach to the colonic mucosa. The mechanism of mucoadhesive polymer is that the excipient will swell and bind to the mucous membrane to stick to the mucosa. The mechanism of the mucoadhesive system can be illustrated in Figure 3. Mucoadhesion is crucial in colon drug delivery as it enhances drug retention in the colonic mucosa, leading to prolonged contact time and potentially improved drug absorption. Upon administration, the mucoadhesive drug formulation reaches the colonic mucosa. The formulation comes into direct contact with the mucus layer lining the colon. Mucoadhesive polymers in the formulation swell upon contact with the mucosal surface. This swelling increases the surface area of the polymer in contact with the mucus. The swollen mucoadhesive polymer forms physical and chemical bonds with the mucous membrane. These bonds can include hydrogen bonds, van der Waals forces, and ionic interactions. The binding mechanism slows down the movement of the drug formulation, leading to prolonged residence time in the colon. This extended contact enhances drug absorption and efficacy. As the formulation remains in contact with the mucosal surface, the drug is gradually released. The prolonged interaction facilitates sustained drug release in the targeted area.

This mucoadhesive property can increase drug release because it can slow down the retention time of the drug in the colon. At neutral pH, the charge of polysaccharides can interact electrostatically with the mucous membrane so that it has higher mucoadhesive properties than at acidic pH [85]. At neutral

Table 3. Colonic enzyme degradation of polysaccharide excipients.

Excipient	Enzyme	Bacteria	Reference
Alginate	Alginate Lyase	<i>Bacteroides</i>	[158]
Amylose	<i>Starch-degrading enzymes</i>	<i>Bacteroides, Bifidobacterium</i>	[67]
Arabinoksilan	β -xylosidase, xylanase	<i>Bacteroides, Bifidobacterium</i>	[39]
Dextran	dextranase	<i>Bacteroides</i>	[71]
Guar Gum	β -mannanase, galactomanase, α -galactosidase	<i>Bacteroides ovatus</i>	[52]
Inulin	inulinase	<i>Bifidobacterium</i>	[77]
Carrageenan	not specific	<i>E. coli</i>	[159]
Chitosan	Lyzosim chitinase	<i>Bacteroides</i>	[160]
Chondroitin Sulfate	chondroitinase	<i>B. thetaiotaomicron, B. ovatus</i>	[50]
Lactulose	β -galactosidase	<i>Lactobacillus, Bifidobacterium</i>	[91]
Locust Bean Gum	β -mannanase, β -mannosidase, α -galactosidase	<i>Bacteroides, Ruminococci</i>	[93]
Pectin	pectinase	<i>Bacteroides</i> <i>Bifidobacterium</i> <i>Eubacterium</i>	[135]
Cyclodextrins	α -amylase, carboxylesterase	<i>Bacteroides</i>	[59]

pH, the charges on polysaccharides interact more effectively with the charged groups on the mucosal surface, enhancing adhesion. Moreover, neutral pH conditions can facilitate better hydration and swelling of mucoadhesive polymers, improving their ability to form strong bonds with the mucus.

Enzymatic degradation

The drug delivery system targeted to the colon uses a degradation mechanism by the microflora in the colon, requiring coating with polysaccharides. The mechanism of this delivery is that polysaccharides will expand and be degraded by enzymes secreted by microflora in the colon. When the drug reaches the colon, the microflora in the colon will secrete enzymes to break down the excipients so that the drug can be released from the system [4]. Examples of excipients that have a mechanism for delivering degradation by microflora in the colon include alginate, amylose, arabinoxylan, dextran, guar gum, inulin, carrageenan, chitosan, chondroitin sulfate, lactulose, locust bean gum, pectin, and cyclodextrin.

The mechanism of CDDS using polysaccharide class excipients is enzymatic degradation by microflora in the colon. The polysaccharides used cannot be degraded in the upper gastrointestinal tract but these polymers are degraded by specific enzymes produced by the colonic microflora. Polysaccharides will be hydrolyzed by enzymatic reactions in the colon and the glycosidic bonds in polysaccharides are broken into saccharides so that the drug can be released from the polysaccharide matrix [30,31]. Some of the polysaccharides that are degraded by enzymes secreted by the colonic microflora can be seen in Table 3.

Prodrug system

A prodrug is an inactive form of a drug that has no pharmacological action but can be converted to its active form in the gastrointestinal tract. When it reaches the colon, the prodrug

will be degraded by specific enzymes secreted by bacteria in the colon, such as dextran by dextranase, pectin by pectinase, and cyclodextrin by α -amylase and carboxylesterase. Following the degradation by bacterial enzymes in the colon, the hydrogen bonds between the drug and the conjugate will be hydrolyzed into saccharide conjugates, then the drug can be released in its active form [41,59,73,100]. The prodrug system can be used as a drug delivery system targeted to the colon by a metabolism mechanism or activation by enzymes in the colon. Prodrug is another form of drug that has a lower pharmacological effect than its original form but can be activated into its original form. Prodrugs can be formed by encapsulating the drug with a conjugate so that a bond occurs between the drug and the conjugate [157]. Examples of excipients that have a mechanism for delivering degradation by microflora in the colon include dextran, chitosan, chondroitin sulfate, pectin, and cyclodextrin.

For instance, Metronidazole made as a prodrug with pectin released 1% to 5% of the drug in pH 1.2 media for 2 hours and pH 6.8 for 6 hours and increased at pH 7.0 with a rat cecal content of 67.9% for 8 hours. The presence of enzymatic degradation by bacteria in the colon causes the release of the drug from its conjugate bond [100]. In another study, the release of 4-amino salicylic acid prodrug conjugated with β -cyclodextrin showed that there was a release of 20%–23% in the stomach and small intestine and 92% release in the colon for 8 hours. This shows that the prodrug is not able to deliver the drug completely to the colon even though the highest percentage of drug release is in the colon. Therefore, it is necessary to add other excipients such as enteric polymers to prevent drug release before reaching the colon [161].

DRUG RELEASE KINETICS FROM POLYMER MATRIX

The factors of drug release can be related to the dissolution and diffusion processes. The coating concentration can affect the release of the drug from the polymer matrix

[139]. Based on the Noyes-Whitney/Nernst-Brunner equation (Equation 2), higher coating concentrations increase the thickness of the diffusion layer around the drug. According to the Noyes-Whitney/Nernst-Brunner equation, a thicker diffusion layer reduces the dissolution rate of the drug, as the drug should diffuse through a greater thickness of coating material. Moreover, as coating concentration increases, the dissolution rate decreases due to the increased barrier for drug diffusion. This can be advantageous for controlling the release rate. Furthermore, achieving sink conditions, where the drug concentration in the solution is maintained at a lower level, can help facilitate continuous drug release by maintaining a concentration gradient [20].

$$\frac{dW}{dt} = \frac{DS}{h} (C_s - C) \quad (\text{Equation 2})$$

where dW/dt is the dissolution rate (g/sec), W is the mass of the drug dissolved in time (t), D is the diffusion coefficient ($\text{cm}^2/\text{second}$), S is the surface area (cm^2), h is the membrane thickness (cm), C_s is the saturated drug concentration (g/cm^3), and C is the drug concentration in solution at time t (g/cm^3).

The release of drugs from the targeted delivery system to the colon will protect or prevent the premature release of drugs in the stomach and small intestine as well as increase the release of drugs in the colon. The ideal drug release profile for a CDDS is to have a time lag. This time delay is due to the presence of drug coating so the drug takes time to diffuse through the polymer matrix. The ideal delay for CDDS is when the drug reaches the colon in the range of 6 to 8 hours after drug administration. But in reality, drug release in the targeted drug delivery system to the colon can also have a burst effect. The burst effect that occurs at acidic pH is an indicator that there is drug release in the stomach so that the drug delivery system fails to deliver the drug to the colon [139]. This often indicates that the coating is insufficient or not properly designed to withstand the acidic conditions of the stomach, leading to failure in targeting the colon effectively. Therefore, the Noyes-Whitney/Nernst-Brunner equation helps quantify this balance, highlighting the trade-offs between coating thickness and dissolution rates, which directly affect the effectiveness of drug delivery to the colon.

CONSIDERATION FACTORS IN COLON DRUG DELIVERY SYSTEM

Selection of appropriate excipients for CDDS

The choice of excipients affects drug release profiles, stability, and effectiveness. Excipients must be compatible with the active drug to ensure drug stability and avoid undesirable interactions. The selection of appropriate excipients for CDDS can also help in designing systems that can deliver drugs specifically to the colon, overcoming challenges such as premature drug release and variable gastrointestinal conditions. Therefore, the selection of appropriate excipients for CDDS should consider the physicochemical properties of active substances and excipients, the approach to delivery mechanisms, drug and excipient stability, and interactions between drugs and excipients.

Polysaccharide group excipients have several main mechanisms, such as swelling, mucoadhesive, prodrug, and degradation by colonic microflora enzymes. In general, the main mechanism of drug release using polysaccharide excipients occurs due to degradation by enzymes secreted by microflora in the colon. Apart from that, polysaccharide excipients have a swelling or swelling mechanism, such as alginate, amylose, guar gum, pectin, and others, allowing the drug to be released by the principle of diffusion or relaxation of the polymer matrix. Polysaccharides that have a mucoadhesive mechanism, such as alginate and chitosan, are often used to formulate drugs for IBD or local drugs to increase the retention time of drugs in the colon. Polysaccharides often form prodrugs such as dextran, chitosan, chondroitin sulfate, pectin, and cyclodextrin. The formation of a prodrug aims to minimize drug absorption at other sites before it reaches the colon by increasing the hydrophilicity of the drug and/or the size of the drug molecule.

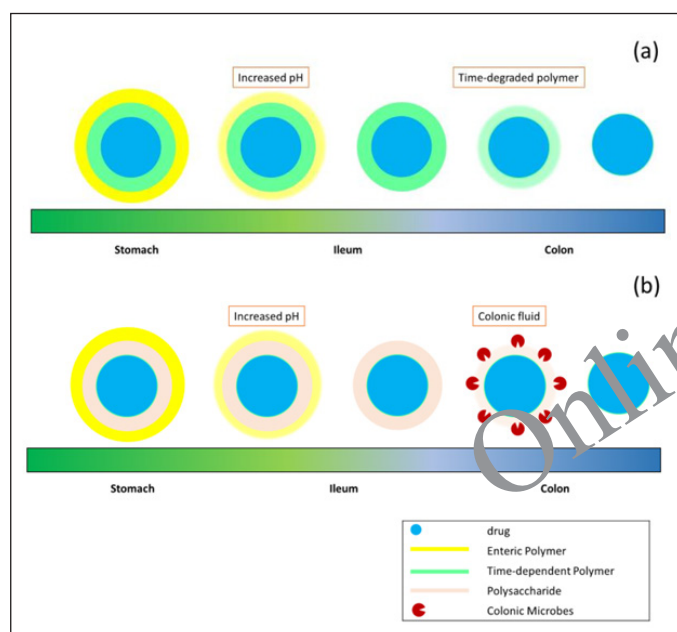
Polymer group excipients have several main mechanisms, such as pH-dependent, time-dependent, and biodegradable. The use of pH-dependent excipients such as HPMCP, HPMCAS, CAP, CAT, Eudragit L, Eudragit S, and others aims to protect and prevent drug release in acidic pH (stomach) so that drug absorption does not occur in the upper gastrointestinal tract. The use of excipients intended for time-dependent releases, such as Kollicoat Smartseal 30D, Eudragit RL, Eudragit RS, Ethyl Cellulose, and HPMC, aims to increase the delay time or time lag of drug release and regulate drug release gradually. Biodegradable excipients such as PLGA have a release mechanism, namely erosion or degradation of the polymer, which aims to control the release of the drug so that there is no sudden large release.

Selection of the concentration of excipients used in the formulation for CDDS

Furthermore, the concentration of excipients used is very influential in drug release. According to the Noyes-Whitney/Nernst-Brunner equation (Equation 2), the increased concentration of excipients can prolong drug release time and even inhibit drug release. Nevertheless, the excipient concentration that is not sufficient will cause a burst effect. The burst effect can also be caused by an imperfect coating process so that there is no drug trapped in the polymer matrix [139]. The Noyes-Whitney/Nernst-Brunner equation is crucial for understanding how excipient concentration affects drug release, as it relates the rate of dissolution to the thickness of the diffusion barrier and the concentration gradient. Key parameters include the diffusion coefficient, surface area, and thickness of the coating, where a thicker barrier (from a higher excipient concentration) can slow drug release, while a thinner barrier (from a lower concentration) may lead to premature release. If the concentration of excipients is too high, it can create a thicker diffusion barrier. This often results in slower or incomplete drug release because the thicker barrier slows down the diffusion of the drug through the coating. Conversely, if the concentration is too low, the coating may be inadequate. This can lead to premature or burst release of the drug, as the

Table 4. Polysaccharide and polymer combination for CDDS.

Drug model	Polysaccharide	Polymer	References
Tetrandrine	Calcium Alginate	CAP	[63]
Curcumin	Guar gum	Eudragit L100	[162]
Ibuprofen	Inulin	Shellac	[164]
5-FU	Chitosan	Poly acrylic acid	[165]
Tetrandrine	Tripolyphosphate chitosan	CAP	[86]
Aceclofenac	Chondroitin Sulfate	Eudragit L100, Eudragit S100	[50]
Budesonid	Lactulose	Eudragit E100, Eudragit FS30D	[76]
5-FU	Locust bean gum	HPMC	[95]
Nicotine	Calcium pectinate	Eudragit E	[166]
Budesonide	Pectin	Ethyl cellulose, Eudragit RS30D	[58]
Ibuprofen	Cyclodextrins	Ethyl cellulose	[167]
Celecoxib	Cyclodextrins	Eudragit S100	[168]

**Figure 4.** Mechanism of combined excipients for CDDS using (a) enteric and sustained polymers, (b) enteric polymer and polysaccharide.

insufficient coating fails to retain the drug within the matrix effectively.

In addition, several factors should be considered in preparing the coating solution for CDDS, which are the type of solvent, the concentration of excipients in the coating solution, and the concentration of the coating solution used in the formulation. The choice of solvent can affect the solubility and dispersion of excipients. Solvents must dissolve the excipients adequately and ensure a uniform coating. Moreover, the concentration in the coating solution determines the thickness and effectiveness of the coating. Higher concentrations can produce thicker coatings, which might delay drug release, while lower concentrations might result in inadequate coatings. Furthermore, the concentration of the final coating solution used

during the coating process affects the uniformity and adherence of the coating.

Utilization of a combination of excipients for CDDS

Additionally, the use of a combination of excipients, such as polysaccharides with enteric polymers, can prevent a burst effect in the stomach and small intestine and can increase the delay time and effectiveness of CDDS. The combination of polysaccharides and polymers is currently widely developed to overcome some of the drawbacks of each excipient. The use of a combination of polysaccharides and polymers is used to protect early drug release in the stomach [162]. In addition, the use of this combination also prevents early drug release that occurs in the small intestine before reaching the colon where the small intestine has a slightly more alkaline pH condition compared to the colon [163].

Some polysaccharides cannot be used alone for a targeted colonic drug delivery system because they release the drug in the upper gastrointestinal tract before it reaches the colon, although perhaps the highest percentage of drug released is in the colon [59,79,60,164]. Several studies using a combination of polysaccharides and enteric polymers can be seen in Table 4. In addition, the combination of polymers with polymers can also be utilized, such as combinations of time-dependent polymers (Eudragit RS or RL) with pH-dependent polymers (Eudragit L or S or FS). This is used to prevent premature release of drugs in both the stomach and small intestine, thereby increasing the effectiveness of the drug delivery system to the colon. The mechanism of the combination of enteric and sustained polymers or enteric polymer and polysaccharide can be seen in Figure 4(a) and (b), respectively.

One of the drug delivery systems to the colon using a combination of polymers and polysaccharides is the Novel CODES™. This system consists of polysaccharides (lactulose), acid-soluble polymers (Eudragit E), and enteric polymers (Eudragit L). Enteric polymers will protect the drug from being released in the stomach, but when it reaches the small intestine, the enteric polymer will dissolve rapidly. In the small intestine,

acid-soluble polymers will prevent the release of the drug until it reaches the colon. When the drug is in the colon, the microflora in the colon will degrade lactulose into lactic acid and dissolve the acid-soluble polymer so that the drug can be released [4, 169].

Excipient modification for CDDS

Several modifications to the excipient used in targeted colonic drug delivery systems can be utilized to increase the effectiveness of CDDS. Modification of these excipients can improve their functional properties and/or improve other properties. Esterification involves reacting excipients with acids to modify their chemical properties. For example, hydroxypropyl methylcellulose acetate succinate (HPMCAS) is created by esterifying hydroxypropyl methylcellulose (HPMC) with anhydrous acetic acid and succinic anhydride. This modification results in a polymer with improved enteric properties, allowing it to withstand acidic conditions in the stomach and dissolve in the more alkaline environment of the intestine [111]. Another modification, the ionic Gelation uses ionic interactions to form a gel network within excipients. For instance, chitosan triphosphate-tetrandrine beads utilize ionic gelation to create a polyelectrolyte complex. This method enhances gel stability and swelling properties, which can improve drug retention and release profiles in the colon. Iswandana *et al.* have developed Chitosan Triphosphate-Tetrandrine beads using ionic gelation to increase polyelectrolyte bonds that intensify the gel formed [86].

Evaluation for CDDS

The evaluation should be conducted to prove the effectiveness of CDDS such as development or swelling studies [79,81], and drug release both *in vitro* [54] and *in vivo* evaluation [66,73]. *In vitro* studies measure drug release and kinetics under controlled conditions, which can be utilized to optimize the formulation. Moreover, *in vivo* studies confirm how the CDDS performs within a complex gastrointestinal environment. *In vitro-in vivo* correlation (IVIVC) can show an association between drug release both *in vitro* and *in vivo* or absorption of drugs in the systemic circulation [58,86,95]. One of the IVIVC studies was carried out using prednisolone core tablets and tablets that had been coated with carboxymethyl xanthan gum and sodium alginate as a delivery system to the colon. There was a good linear correlation ($r = 0.997$) between the cumulative percentage of drug released *in vitro* from the core tablet and the percentage of drug absorbed *in vivo*. Meanwhile, tablets that had been coated for delivery to the colon had a poor correlation ($r = 0.842$) between the cumulative percentage of drug released and the percentage of *in vivo* drug absorbed. However, the cumulative percentage of colon-targeted drug released *in vitro* with the percentage of *in vivo* drug absorbed has a good correlation after a delay time of 360 minutes indicating drug release in the colon [152]. IVIVC can correlate between *in vitro* drug release data with *in vivo* drug absorption to predict clinical outcomes. A strong IVIVC,

such as the one observed with prednisolone tablets, indicates that *in vitro* results can reliably forecast *in vivo* performance. This correlation aids in predicting plasma drug concentrations and therapeutic effectiveness.

Based on the IVIVC, the plasma concentration over time can be predicted which can be clinically meaningful from *in vitro* studies. However, in the IVIVC prediction, there may be some variations that can be caused by dissolution testing not clearly describing conditions in the gastrointestinal tract, such as transit time, pH, content, fasting conditions, number of microbes, enzymes, enterohepatic cycle, and first-pass metabolism. IVIVC predictions can also be affected by variations in gastrointestinal conditions, such as pH and enzyme activity, and individual physiological differences. These factors can lead to discrepancies between *in vitro* and *in vivo* results, highlighting the need for improved testing conditions and integration of both data types for accurate predictions. Therefore, the improved *in vivo* testing models that more accurately mimic human gastrointestinal conditions can help in better evaluating the performance of CDDS formulations. This can lead to more effective and safer drug delivery systems.

Future Perspective

CDDS has a very promising strategy for enhancing the oral drug delivery system which can increase the bioavailability of drug via targeting delivery to the colon. However, to enhance the effectiveness of CDDS, novel excipients with improved properties should be discovered and synthesized that offer better performance in diverse gastrointestinal environments and can lead to more effective CDDS formulations. Furthermore, the advanced drug delivery system, including the use of advanced nanocarriers and smart polymers, could offer improved precision in drug delivery. In addition, CDDS could also have a potential for personalized medicine approaches tailored to individual patient needs by considering genetic, physiological, and lifestyle factors that can optimize therapeutic outcomes. Personalized approaches could involve designing excipients that respond to specific biomarkers or conditions unique to individual patients. Some techniques such as 3D printing and microencapsulation may provide more customized and efficient drug delivery systems.

CONCLUSION

CDDS requires excipients that have specific characteristics to protect the drug released in the stomach and small intestine and increase the release of the drug in the colon. Polysaccharides have mechanisms including swelling and can be degraded by enzymes produced by colonic microflora which can facilitate the drug release in the colon site. Meanwhile, polymer-based excipients typically release the drug in the colon site through pH-dependent, time-dependent, or biodegradable mechanisms via diffusion release. Effective CDDS requires careful selection and optimization of these excipients. However, the implementation of these excipients presents challenges, including the complexity of formulation and the need for multiple excipients to address various biopharmaceutical needs.

Therefore, future research should focus on refining excipient combinations, exploring novel polymers and polysaccharides, and addressing practical challenges in formulation by using advanced drug delivery systems.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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