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Polysaccharides: a targeting strategy for colonic drug delivery

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Introduction: Colon targeting has gained increasing importance for the topical treatment of diseases of the colon, such as Crohn's disease, ulcerative colitis, colorectal cancer and amebiasis. Various strategies used for targeting drugs to the colon include formation of a prodrug, coating with time or pH-dependent polymers, use of colon-specific biodegradable polymers, osmotic systems and pressure-controlled drug delivery systems. Among the different approaches used, polysaccharides that are precisely activated by the physiological conditions of the colon hold great promise, as they provide improved site specificity and meet the desired therapeutic needs.

Areas covered: This review aims to summarize the natural and modified properties of polysaccharides that are responsible for their colon targeting abilities. Emphasis is placed on describing formulation approaches that use polysaccharides as a strategy for targeting drugs to the colon.

Expert opinion: Polysaccharide-based colon-targeted drug delivery systems are effective when they are precisely activated by the physiological conditions of the colon. Absence of enzymes during colonic disorders might hinder the activation of the delivery system. To guarantee delivery of the drug to the colon, it is preferable to combine polysaccharides with enteric or cellulose polymers.

Keywords: compression coated, hydrogel, physiological conditions, polysaccharides, transit time

Expert Opin. Drug Deliv. (2011) 8(6):779-796

1. Introduction

The oral route of administration is considered to be the most convenient and commonly used method for drug delivery. Conventional oral dosage forms have traditionally been designed to dissolve drug in the upper part of gastrointestinal tract (GIT) and for it to be absorbed from these regions, depending on the physicochemical properties of the drug. Problems arise when local targeting is desired to the distal part of GIT such as the colon or in conditions where a drug needs to be protected from the acidic environment of the stomach [1]. Targeting of drugs to the colon is of increasing importance for local treatment of inflammatory bowel diseases (IBD) of the colon, such as ulcerative colitis and Crohn's disease [2,3]. The prevalence of ulcerative colitis and Crohn's disease ranges from 10 to 70 per 100,000 people, but recent studies in Manitoba, Canada and Rochester, MN, have shown the prevalence to be as high as 200 per 100,000 people [4,5].

The colon presents less hostile conditions for drug delivery because it is less diverse and has a lower intensity of enzymatic activity and a near neutral pH [6]. The major function of the colon is to absorb water and electrolytes (each day up to 2000 ml of fluid enters the colon through the ileocecal valve). The absorption capacity of the human colon is lower than that of the small intestine, but the residence time of the formulations is as high as 2 – 3 days, which may vary in diseased condition such as IBD. This long residence time provides a significant opportunity for the absorption of drugs [7-9]. Most of the previous colon targeting systems focused on one of the following three approaches: pH-dependent release,

10.1517/17425247.2011.574121 © 2011 Informa UK, Ltd. ISSN 1742-5247

Article highlights.

- The residence time of formulations in the colon is 2 – 3 days, which provides a significant opportunity for the absorption of drugs.
- Polysaccharides, when used orally, are specifically degraded in the colon owing to the presence of a variety of bacterial species.
- To impart more specificity to the polysaccharide-based drug delivery system, extra protection is provided by the addition of some more release-controlling excipients to the system.
- The use of naturally occurring dietary polysaccharides as a drug carrier for colonic delivery simplifies the issues of safety, toxicity and availability.

This box summarizes key points contained in the article.

time-dependent release, or bacterial degradation in the distal ileum/colon with limited *in vivo* evaluation. Colonic delivery systems based solely on time or pH dependency of release are not reliable because of the inherent variability of pH and transit times through the upper GIT [10,11]. Use of polymers that release the drug at higher pH values (> 7) may fail to release the drug in a reliable way in the colon because pH drops to 6.4 ± 0.6 on entering the colon [6]. With respect to transit times, the small intestinal transit time is fairly constant at 3 – 4 h in most individuals, but gastric emptying is highly dependent on whether the dosage form is ingested in the fed or fasted state, on concomitant fluid intake and, in the fasted state, the extent of the phase of the motility cycle at the time of ingestion. Therefore, site-specific release in the colon cannot be guaranteed by dosage forms that are designed to release the drug a prespecified number of hours after ingestion [12]. Of these three approaches, microflora-activated systems appear to be more promising, as the abrupt increase of the bacterial population and associated enzymatic activity in the colon represent a non-continuous event, independent of the GI transit time [13,14]. The number of microorganisms increases gradually on descending along the small intestine, but it rises by several orders of magnitude beyond the ileocecal valve. This is due to a retardation of movement of the contents within the gastrointestinal tract resulting from widening of the intestinal lumen as the contents move from the ileum to the cecum and to the ascending colon. These facts and the bag-shaped nature of the cecum make this site the favorite region for microbial settlement. Intestinal microflora count: 10^3 CFU/ml; colonic microflora count: 10^{12} CFU/ml.

About 400 bacterial species such as *Bifidobacteria*, *Eubacteria*, *Bacteroides*, *Clostridia*, and so on, have been found in the colon, which liberate > 500 different types of enzyme [15]. The occurrence of some common bacteria in the GIT is listed in **Table 1**. The energy requirement of colonic bacterial flora for maintaining the cellular function is derived from the fermentation of various substrates that are left indigested in the small intestine. These substrates include di- and trisaccharides, such as raffinose, stachyose, cellobiose and lactulose, and residues of partially digested polysaccharides, such as starch and polysaccharides from endogenous sources such as mucopolysaccharides [16,17]. In addition to polysaccharides, other substrates for fermentation are dietary fibers, which include all the non-α-glucan polymers that originate in the plant cell wall cellulose, hemicellulose and pectin substances [18]. Several enzymes, such as β-D-glucosidase, β-D-galactosidase, β-xylosidase, β-arabinosidase, azoreductase, deaminase, urea hydroxylase and nitroreductase, are produced by colonic microflora to carry out fermentation of these substrates (polysaccharides and dietary fibers) [19,20]. These enzymes, which are derived from microbes, degrade coatings/matrices as well as break bonds between an inert carrier and an active agent, that is, release drug from the polymeric prodrugs.

Ideal candidates for colonic drug delivery are drugs that show poor absorption from the stomach or intestine, and the drugs used in the treatment of IBD, diarrhea and colon cancer. The colon is considered to be the preferred absorption site for oral administration of proteins and peptide drugs owing to relatively low proteolytic enzyme activities in the colon compared with the upper gastrointestinal tract. Potential protein and peptide drug candidates for oral colon-specific drug delivery systems are listed in **Table 2**. Different drugs under research for colonic disorders are mentioned elsewhere [21].

The use of naturally occurring polysaccharides is attracting a lot of attention for targeting drugs to the colon, as these polymers of monosaccharide are found in abundance and are inexpensive. Synthetic polymers are associated with toxic effects and thus extensive research is being carried out to explore the use of natural polymers derived from plants and animals. Natural polymers used for colon-targeted delivery are based on the fact that anaerobic bacteria in the colon are able to recognize the various substrates and degrade them with the enzymes. The natural polymers that are stable in the gastric environment of the upper GIT are preferred for colon-targeted delivery. The basic intention of this review is to focus on the properties of polysaccharide that are responsible for its application as a colon-targeting tool. The review also focuses on current approaches to targeting drug to the colon, using natural polysaccharides as carriers for the active drug.

2. Polysaccharides: characteristics and properties

Major polysaccharides used for targeting drugs to the colon are pectin, guar gum, chitosan, amylose, inulin, locust bean gum, chondroitin sulfate, dextran and alginate. These polysaccharides when used orally are specifically degraded in the colon. To understand the characteristic properties responsible for their colonic degradation is of particular importance when using them as carriers for colon-targeted drug delivery.

Table 1. Gastrointestinal bacterial count in humans.

	Stomach	Ileum	Jejunum	Colon
Aerobic or facultative bacteria				
Staphylococci	0 – 10^2	0 – 10^3	10^2 – 10^5	10^4 – 10^7
Enterobacteria	0 – 10^2	0 – 10^3	10^2 – 10^6	10^4 – 10^{10}
Lactobacilli	0 – 10^3	0 – 10^4	10^2 – 10^5	10^6 – 10^{10}
Streptococci	0 – 10^3	0 – 10^4	10^2 – 10^6	10^5 – 10^{10}
Anaerobic bacteria				
Eubacteria	Uncommon	Uncommon	Uncommon	10^9 – 10^{12}
Clostridia	Uncommon	Uncommon	10^2 – 10^4	10^6 – 10^{11}
Bacteriodes	Uncommon	0 – 10^2	10^3 – 10^7	10^{10} – 10^{12}
Bifidobactrium	Uncommon	0 – 10^3	10^3 – 10^5	10^8 – 10^{12}
Gram-positive cocci	Uncommon	0 – 10^3	10^2 – 10^5	10^8 – 10^{11}

Table 2. Potential protein and peptide drug candidates for oral colon-specific drug delivery system.

Agent	Therapeutic use
Insulin	Type I diabetes
Interferons	Prophylaxis of hepatitis, malignancy
Leuprolide	Infertility, prostrate carcinoma
Ciclosporin	Immunosuppressant
Epoeitin	Anemia associated with chronic renal failure
Amylin	Diabetes and nutrition regulation
Calcitonin	Paget's disease of bone, hypercalcemia
Antisense oligonucleotides	Cancer and AIDS
Filgrastim	Neutropenia
Gonadorelins	Endometriosis, infertility
Glucagon	Chronic intractable hypoglycemia
Desmopressin	Pituitary diabetes insipidus
Vasopressin	Pituitary diabetes insipidus
Somatropin	Turner's syndrome, dwarfism
Salcatonin	Paget's disease of bone, hypercalcemia
Urofollitin	Infertility
Octreotide	Pancreatitis and acromegaly
Sermorelin	Endometriosis and infertility
Etanercept	Rheumatoid arthritis

Chemistry and natural sources of different polysaccharides are listed in **Table 3**. Characteristic properties and polysaccharide-specific modified properties of different polysaccharides are discussed below.

2.1 Pectin

2.1.1 *Natural characteristics*

Pectins are polymers of galacturonic acid linked by α(1–4) bonds, where the carboxyl groups are methylated to varying degrees. However, pectins also contain neutral sugars such as galactose, rhamnose or arabinose, either as part of the polymer backbone (e.g., rhamnose) or as side chains (e.g., arabinose). Neutral sugar side chains tend to be concentrated into particular areas of the pectin molecule described as 'hairy regions', with the sugar-free areas termed 'smooth regions'. In human digestion, pectin more or less passes intact through the small intestine and is degraded by microorganisms present in the colon; but if the number of hairy regions increases the colon-targeting property of the pectins may be hindered, as at low pH (< 2) the hairy regions are less stable compared with smooth regions [22-24].

2.1.2 *Modified characteristics*

2.1.2.1 *Addition of calcium*

Pectin is a soluble dietary fiber, so it led to the development of derivatives of pectin that were less water soluble but were degradable by the colonic microflora [25]. Calcium salts of pectin give a better shielding effect by forming an 'egg-box' configuration, which reduces the solubility of pectin. The amount of calcium present in the formulation should be greatly controlled to provide optimum drug delivery [26].

2.1.2.2 *Degree of esterification and amidation*

The degree of esterification greatly influences the properties of pectin, especially its solubility and its requirements for gelation, which are directly derived from the solubility. In nature, ~ 80% of carboxyl groups of galacturonic acid are esterified with methanol. This proportion is decreased more or less during pectin extraction. The ratio of esterified to non-esterified galacturonic acid determines the behavior of pectin in drug delivery applications. This is why pectins are classified as high-ester pectins (HE) and low-ester pectins (LE). The degree of esterification (DE) varies depending on the source of the pectin and enzymatic activity in the process of ripening and maturation, and the conditions under which the isolation is conducted. Some of the carboxyl groups may be converted to carboxamide groups when ammonia is used in the process of de-esterification, producing amidated pectin. Pectins in which 50% or more of galacturonic acid are esterified are termed HE pectins. The non-esterified galacturonic acid units can be either free acid or salts with sodium, potassium or calcium. The efficiency of a pectin-based colonic system

Table 3. Polysaccharide chemistry and natural source.

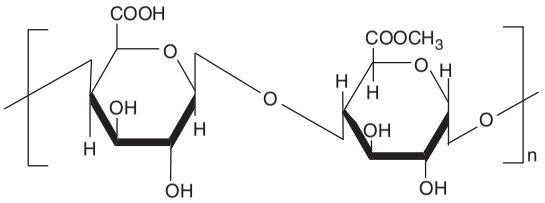
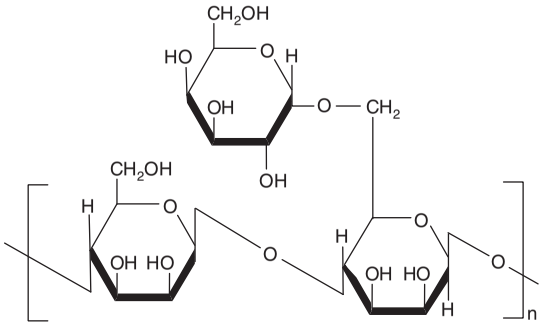
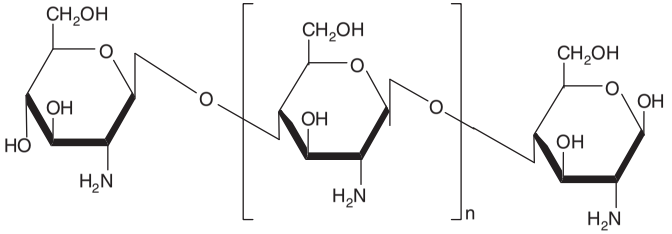
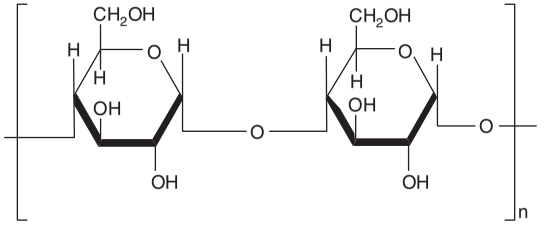
Type of polysaccharide	Structure	Structural unit	Natural source
Pectin		α-(1–4)-linked D-galacturonic acid	Cell wall of higher terrestrial plants, fruits and vegetables
Guar gum		Linear chains of mannose with 1β→4 linkages to which galactose units are attached with 1α→6 linkages	Endosperm of the seeds of *Cyamopsis tetragonolobus*
Chitosan		Copolymer of glucosamine and *N*-acetylated glucosamine	Shell of marine invertebrates
Amylose		Linear polymer of glucose linked mainly by α(1–4) bonds	Storage polysaccharide in plants

Table 3. Polysaccharide chemistry and natural source (continued).

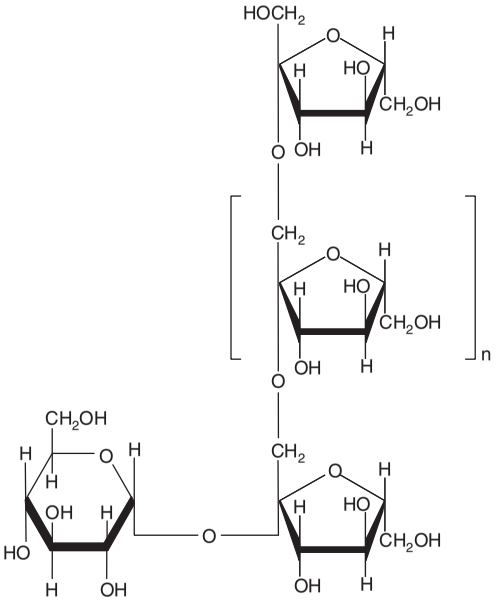
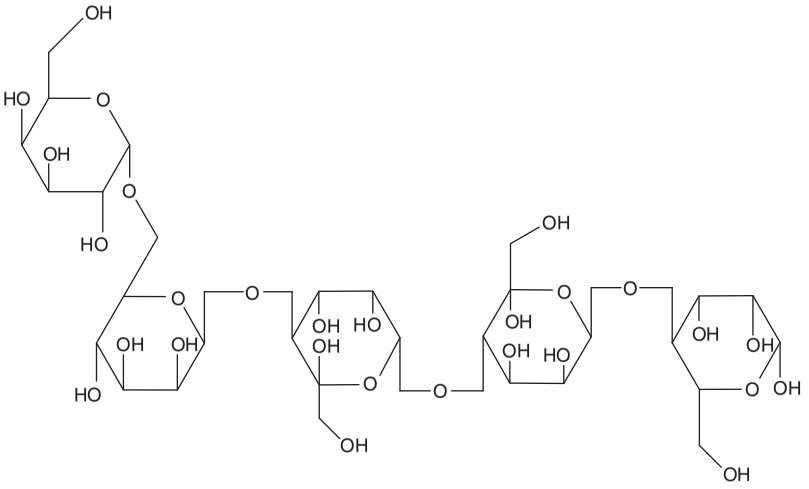
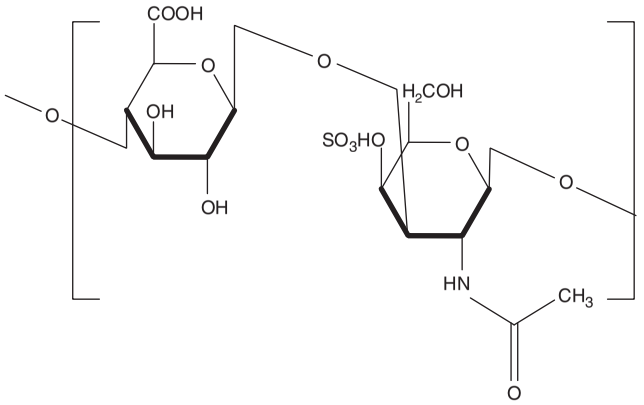
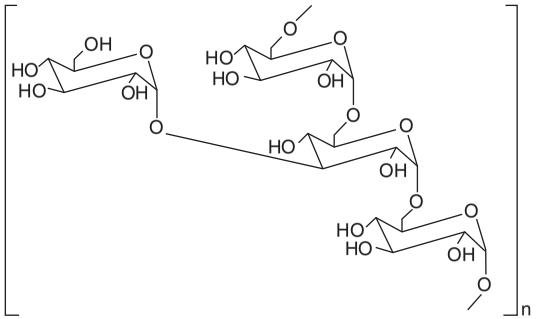
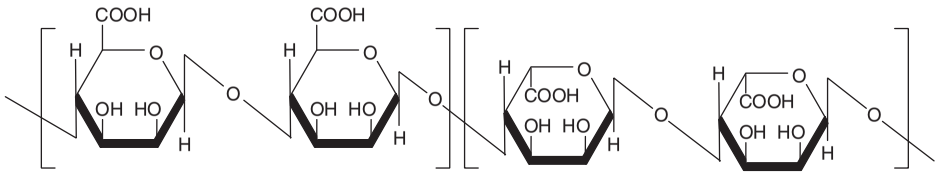
Type of polysaccharide	Structure	Structural unit	Natural source
Inulin		Several simple sugars linked together	Many types of plant
Locust bean gum		β-1,4-D-galactomannan	Derived from carob (*Ceratonia siliqua*) seeds

Table 3. Polysaccharide chemistry and natural source (continued).

Type of polysaccharide	Structure	Structural unit	Natural source
Chondroitin sulfate		D-Glucuronic acid and *N*-acetyl-D-galactosamine	Cartilaginous tissues of many invertebrates
Dextran		α-1,6-D-glucose	Bacterial cultures of *Leuconostoc mesenteroides*
Alginates		Homopolymeric blocks of (1–4)-linked β-D-mannuronate and α-L-guluronate residues	Seaweed

depends on the type of pectin used (HE, LE or amidated). Low-ester pectins form more rigid gels with calcium as compared with HE pectins, whereas amidated pectins are tolerant to pH variations and calcium levels, which make amidated pectins an obvious choice for colonic delivery systems [27,28].

2.1.2.3 Crosslinking of pectin with aldehydes

Glutraldehyde crosslinked calcium pectinate beads successfully delivered resveratrol to the colon. A minimum glutraldehyde concentration and crosslinking time are essential to produce sufficiently strong beads that can prevent drug release in the upper GI tract [29].

2.2 Guar gum

2.2.1 Natural characteristics

Guar gum is used as for delivering drugs to the colon because it retards drug release in the large intestine and is also specifically degraded in the presence of colonic microflora [30]. Guar gum hydrates and swells in cold water, forming viscous colloidal dispersions or sols, which retard drug release from the drug delivery system [31].

2.2.2 Modified characteristics

Owing to rapid swelling of guar gum, there are chances of the drug being released before it reaches the colon. To stop premature drug release, low swelling guar gum was manufactured by crosslinking it with trisodium trimetaphosphate, which was capable of delivering drug to the colon [32].

2.3 Chitosan

2.3.1 Natural characteristics

Chitosan, a linear amino polysaccharide composed of randomly distributed (1–4)-linked d-glucosamine and *N*-acetyl-D-glucosamine units, is obtained by the deacetylation of chitin, a widespread natural polysaccharide found in the exoskeleton of crustaceans such as crab and shrimp. The degree of deacetylation has a significant effect on the solubility and rheological properties of the chitosan. Chitosans with a low degree of deacetylation (≤ 40%) are soluble up to a pH of 9, whereas highly deacetylated chitosans (≥ 85%) are soluble only up to a pH of 6.5. Chitosan is a weak base with a pK_a value in the range 6.2 – 7.0, depending on the source of the polymer [33]. At low pH, the polymer is soluble, with the sol-gel transition occurring at ~ pH 7. Chitosan-based delivery systems can protect therapeutic agents from the hostile conditions of the upper gastrointestinal tract and release the entrapped agents specifically at the colon through degradation of the glycosidic linkages of chitosan by colonic microflora.

2.3.2 Modified characteristics

2.3.2.1 Crosslinking of chitosan solution with aldehydes

Chitosan has often been limited in colonic targeting of drugs because of its high solubility in gastric fluids, sometimes resulting in burst release of the drug at the stomach. Chitosan can be insoluble at acidic fluids through chemical crosslinking with aldehydes [34].

2.3.2.2 Effect of H-bond formation

On granulation of chitosan with poly(vinyl pyrrolidone) (PVP) binders, the solubility of chitosan in the acidic medium decreases. Granulation also enhances the cohesiveness and compressibility of the blended mixture. It enables the formation of an H-bond between PVP and chitosan, leading to increased water absorbability and rapid formation of a gel layer [35]. Yassin *et al.* [36] showed that high coat thickness with granulated chitosan resulted in complete protection against both acidic and alkaline media.

2.4 Amylose

2.4.1 Natural characteristics

This naturally occurring polysaccharide possesses the ability to form films. These films are water swellable and are potentially resistant to pancreatic α-amylase but are degraded by colonic bacterial enzymes [37].

2.4.2 Modified characteristics

One form of starch, amylose, can be made resistant to pancreatic enzymes through the formation of an amorphous structure (amorphous amylose), and can be degraded by colonic bacteria [38]. In its glassy amorphous form, amylose is metabolized by bacterial amylase enzymes of colonic origin. Therefore, on passage through the gastrointestinal tract, glassy amylose will remain intact in the upper gut and then be fermented in the colon.

2.5 Inulin

2.5.1 Natural characteristics

Inulin is indigestible by the human enzymes ptyalin and amylase, which are adapted to digesting starch. As a result, inulin passes through much of the digestive system intact. It is only in the colon that bacteria metabolize inulin. Inulin also stimulates the growth of bacteria in the gut [39]. Major bacteria responsible for fermentation of inulin in colon are *bifidobacteria* [40].

2.5.2 Modified characteristics

The introduction of vinyl groups in this sugar polymer by free radical polymerization formed hydrogels resistant to the upper GIT. Thus, these modified hydrogels can be successfully used as a carrier for drug delivery to the colon [41].

2.6 Locust bean gum

2.6.1 Natural characteristics

Locust bean gum is soluble in water. The hydration capacity of this polymer is lower in cold water, thus it requires heat for full hydration and maximum viscosity [42].

2.6.2 Modified characteristics

Crosslinked galactomannan led to water-insoluble film-forming product-showing degradation in colonic microflora [43].

2.7 Chondroitin sulfate

2.7.1 Natural characteristics

Chondroitin sulfate is degraded by the anaerobic bacteria of the large intestine mainly by *Bacteroides thetaiotaomicron* and *B. ovatus* [44]. Owing to its specificity for degradation towards colonic enzymes, it can be used as a carrier for drug delivery to the colon. However, the high water solubility of chondroitin sulfate is disadvantageous. The use of chondroitin sulfate as a carrier for delivery of indomethacin proved unsuccessful as 100% of the drug released in 1 h [45].

2.7.2 Modified characteristics

To prolong the release it is necessary to use crosslinked chondroitin sulfate, which could prolong drug delivery. Chondroitin sulfate was crosslinked with 1,12-diaminododecane. This crosslinked chondroitin sulfate was used to prepare matrix tablets with indomethacin. The degree of crosslinking chondroitin sulfate affected drug release from its matrices. Higher crosslinking decreased the release, whereas crosslinking in a lower proportion increased release from the matrices [46].

2.8 Dextran

2.8.1 Natural characteristics

2.8.1.1 Hydrolysis of glycosidic bonds

The glycosidic linkages are hydrolyzed by molds, bacteria and also by mammalian cells. Dextranases are the enzymes responsible for hydrolysis of these glycosidic linkages. Dextranase activity of the colon is shown by anaerobic Gram-negative intestinal bacteria, especially the *Bacteroides* [47].

2.8.1.2 High-molecular-mass dextrans

Dextrans are polysaccharides that are suitable for colon drug delivery, especially the high-molecular-mass types, which are less soluble in aqueous media. Tablet formulation of solid dispersions of budesonide with dextran in the ratio 1:7 and using molecular mass of 10,000 of dextran represented an effective tool for the treatment of colonic inflammatory bowel disease [48].

2.8.2 Modified characteristics

To impart colon specificity, low-molecular-mass natural dextrans can be converted to high-molecular-mass dextrans by synthetic modifications. Bauer and Kesselhut [49] synthesized dextran fatty acid ester and concluded that lauroyl dextran esters with molecular mass of ~ 250,000 and degree of substitution ranging from 0.11 to 0.3 were suitable for colon drug delivery as film coatings. For theophylline as drug, Hirsch and co-workers [50,51] demonstrated that for lauroyl dextran esters having degree of substitution between 0.12 and 0.40, the release rate (*in vitro*) was inversely proportional to coat thickness. The addition of dextranase to the dissolution medium increased the degradation rate of dextran.

2.9 Alginates

2.9.1 Natural characteristics

Sodium alginate is a linear copolymer consisting of β-(14) mannuronic acid and α-(14) l-guluronic acid residues. In general, gel formation of polysaccharides in the gastric medium prevents drug release from the core. Alginates do not gel because they have rigid poly(l-guluronic acids), which gel in the presence of Ca^{2+} ions [52]. Thus, alginates without the presence of Ca^{2+} ions cannot be used as a colonic carrier.

2.9.2 Modified characteristics

Alginate gelation takes place when divalent cations (usually Ca^{2+}) interact ionically with blocks of guluronic acid residues, resulting in the formation of a three-dimensional network that is usually described by an 'egg-box' model [53]. It is the ion exchange process between Na^{+} and Ca^{2+} ions that is supposed to be responsible for the swelling and subsequent degradation of sodium alginate in the colon. The mechanical and swelling properties of swelled alginate, produced by ionic crosslinking with cations, depend on several factors, such as valency of ions, size of ions, and so on. For example, monovalent cations and Mg^{2+} ions do not induce gelation [54], whereas Ba^{2+} ions produce stronger beads than Ca^{2+} [55]. Modifying the release properties by calcium addition is possible only in pectin and alginate-based systems.

3. Approaches for colon-targeted drug delivery

All polysaccharides discussed in this review show colon-specific degradation, but to impart more specificity to the delivery system an extra protection is provided by the addition of some more release-controlling excipients to the system. The colonic system can be prepared by either the combination of different polysaccharides or the combination of natural polysaccharide with synthetic polymers. Some commonly used approaches based on this fundamental are discussed below.

3.1 Prodrug-based formulations

A colon-targeted prodrug is a pharmacologically inert form of an active drug that must undergo transformation to the parent compound in the colon by either a chemical or an enzymatic reaction to exert its therapeutic effect. Site-specific drug delivery through site-specific prodrug activation may be accomplished by some specific property at the target site, such as altered pH or high activity of certain enzymes relative to the non-target tissues for the prodrug–drug conversion. The prodrug approach has been explored for pectin-, inulin- and dextran-based systems.

3.1.1 Pectin-based prodrugs

Ketoprofen was directed to the colon by preparing a pectin-ketoprofen complex that acted as a prodrug. *In vivo* studies in rats demonstrated that ketoprofen was distributed mainly in the cecum and the colon [56].

3.1.2 Inulin-based prodrugs

Methacrylated inulin hydrogels were successful at targeting proteins to the colon. The feed composition and degree of substitution of inulin seemed to be crucial in controlling the extent and rate of drug release [57]. Colon-targeted inulin hydrogel was prepared by combining methacrylated inulin (MA-IN), aromatic azo agent bis(methacryloylamino)azobenzene (BMAAB) and 2-hydroxyethyl methacrylate (HEMA) or methacrylic acid (MA). Uptake of water in the gels was inversely proportional to the MA-IN feed concentration, the degree of substitution of the inulin backbone, and the concentration of BMAAB. On using prednisolone as a model drug it was found that on increasing HEMA or MA, drug release greatly increased, and on decreasing HEMA or MA, drug release decreased [58].

3.1.3 Dextran-based prodrugs

The first attempt to prepare dextran-based prodrug was made by Harboe and co-workers [59,60], who conjugated naproxen to dextran by ester linkage. When ketoprofen and naproxen were linked with dextran they showed specific release in the colon of pigs. The release of naproxen was up to 17 times higher in homogenates of cecum and colon as compared with control medium or homogenates of the small intestine. Glucocorticoids such as methyl prednisolone and dexamethasone are an effective therapy for colitis. As these glucocorticoids do not have a functional group for attachment to dextrans, they were attached to dextrans using a spacer molecule. It was found that dextran conjugates showed little hydrolysis in the upper GIT contents, but were degraded rapidly in the cecal and colonic contents [61]. Budesonide-dextran conjugates were effective at improving signs of inflammation in an experimental model of colitis [62].

3.2 Drug in capsule approach

Filling a capsule with the drug is the easiest way of administering drug to the colon. Two different approaches have been tried for these systems: i) filling the drug in polysaccharide capsules with an extra enteric coating, if required; and ii) filling the drug in gelatin/hydroxypropyl methylcellulose (HPMC) capsules with an extra polysaccharide coating to provide colon specificity.

3.2.1 Chitosan capsules

Using male Wistar rats as an animal model, Tozaki *et al.* [63] compared the healing effect of chitosan capsules containing a new thromboxane synthase inhibitor (R68070) on ulcerative colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) with that of a carboxymethylcellulose (CMC) suspension of R68070. Chitosan capsules provided higher concentrations of R68070 in the large intestine than the CMC suspension. In another similar study by the same group [64], the authors used the same animal model to investigate the healing effect of chitosan capsules containing 5-aminosalicylic acid (5-ASA) on TNBS-induced ulcerative colitis. Chitosan capsules loaded with 5-ASA provided higher therapeutic effect than the 5-ASA-CMC suspension.

Hydroxypropyl methylcellulose phthalate, an enteric-coating material, was used to coat chitosan capsules loaded with insulin. Using male Wistar rats, insulin-containing chitosan capsules were administered orally with a total dose of 20 IU into the stomach with polyethylene tubing. The hypoglycemic effect started 6 h after administration, when the capsules were in the colon, and lasted for 24 h [65].

3.2.2 Dextran capsules

Hydrocortisone containing glutaraldehyde crosslinked dextran capsules were prepared by Brondsted *et al.* [66]. *In vitro* release studies carried out in pH 5.4 in the absence of enzymes showed only 10% release in the first hour and 35% up to 24 h. Addition of dextranases to dissolution medium after 24 h resulted in fast degradation of capsules, resulting in almost complete release of hydrocortisone [66].

3.2.3 Polysaccharide-coated HPMC capsules

HPMC capsules coated with a mixture of amylose and ethylcellulose were used to deliver 4-aminosalicylic to the colon. *In vivo* studies revealed that amylose coatings can successfully deliver 4-aminosalicylic acid to the colon for treatment of inflammatory bowel disease [67].

3.3 Matrix tablets

Polysaccharide-based matrix tablets are the simplest and most versatile mode of achieving colon specificity. Almost all the polysaccharides have been explored for their use as matrix systems. The basic drawback of this system is that they need an extra barrier coat in the form of a compression coat or an enteric coat to prevent premature drug release. A few colonic matrix systems explored are listed below.

Indomethacin matrix tablets were prepared using guar gum as a carrier. These tablets retained their integrity for a total of 5 h, which included 2 h exposure in 0.1 M HCl and 3 h exposure in Sorensen's phosphate buffer (pH 7.4). The total drug released after 5 h was 21%, which is a high amount of drug being released before the tablet reaches colon [68]. Guar gum-based colon-targeted matrix tablets of rofecoxib were prepared using 40, 50, 60 and 70% guar gum. *In vivo* evaluation in human volunteers showed delayed T_{max}, prolonged absorption time (t_a), decreased C_{max} and decreased absorption rate constant (ka) as guar gum concentration increased from 40 to 70% [69]. Matrix tablets were also prepared for celecoxib and mebendazole using guar gum as a carrier. *In vitro* studies reveal that matrix tablets containing either 20 or 30% of guar gum are most likely to target both the drugs for local action in the colon [70,71].

Colon-specific drug delivery systems for mesalazine were prepared using locust bean gum and chitosan in the ratios 2:3, 3:2 and 4:1. *In vivo* studies carried out in nine healthy male human volunteers for various formulations revealed that drug release was initiated only after 5 h, which is the

transit time of the small intestine. The formulation containing locust bean gum and chitosan in the ratio 4:1 held a better dissolution profile and higher bioavailability [72].

3.4 Mixed film coatings

Films made from polysaccharide lack the strength required to keep them intact for 5 – 6 h in the GIT (considered as the lag time required for reaching the colon). Thus, addition of another coating polymer in the same coat would provide tensile strength sufficient to obtain the desired lag time. The extra coating polymer may consist of another polysaccharide, or a hydrophilic or hydrophobic polymer.

3.4.1 *Ethylcellulose-based films*

Addition of a hydrophobic polymer such as ethylcellulose is highly recommended to increase the tensile strength of the films and restrict the entry of water and the consequent swelling of the polymer to alter the solubility of the polymer.

3.4.1.1 *Pectin-ethylcellulose films*

First, pectin-ethylcellulose films were successfully developed on paracetamol cores. The study concluded that drug release from the core was dependent on the pectin-ethylcellulose ratio and coating level [73]. Pectin and ethylcellulose were used in a single film coat to target 5-fluorouracil pellets to the colon. At 1:2 ratio of pectin:ethylcellulose almost 80% drug release was found in the colon [74]. The pectin/Kollicoat® (BASF, Germany) SR30D mixed films were susceptible to rat colonic bacterial enzymes and were completely degraded in the colitis-induced rats. The extent of digestion correlated with the amount of pectin present within the film [75].

3.4.1.2 *Guar gum-ethylcellulose films*

To prevent premature release in the small intestine a combination of guar gum and ethylcellulose was used to coat 5-fluorouracil pellets. *In vitro* release studies indicated that addition of hydrolase enzyme to dissolution medium (pH 6.5 phosphate buffer) accelerated release of drug from the formulation. It was concluded that a mixed coating of guar gum and ethylcellulose prevents drug release in the stomach and allows enzymatic breakdown of the coat to release drug in the colon [76].

3.4.1.3 *Amylose-ethylcellulose films*

Addition of ethylcellulose to an amylose coating solution increased the tensile strength of the amylose films [77]. When amylose and ethylcellulose were tried as a film coat for formulating colonic tablets of mesalazine, it was found that the rate and extent of drug release were inversely proportional to the amount of ethylcellulose in the film coat and the thickness of the coat. Drug release increased in the presence of cecal content, indicating susceptibility of amylose to colonic microflora [78]. In another study, 5-ASA pellets were coated with aqueous dispersion of amylose and Ethocel® (Colorcon, USA). The optimum coating formulation consisted of amylose:Ethocel in 1:4 w/w ratio. At this ratio the drug release was suppressed for 12 h in simulated gastric and intestinal fluids. On introduction of these coated pellets in simulated colonic fluids the coat fermented and released the drug within 4 h [79]. This study was extended further where glucose was used as a model drug. Here also a 1:4 w/w ratio of amylose: Ethocel was found to be optimum [80].

3.4.2 *Miscellaneous mixed films*

To provide mechanical strength to polysaccharide films, polysaccharides can be mixed with insoluble grades of Eudragit® (Evonik, Germany) such as Eudragit®RL/RS. Study of theophylline release from pellets coated with pectin HM:Eudragit®RL:Eudragit®NE ternary mixtures has shown that the presence of pectinolytic enzymes in the dissolution media results in an increase of the drug release rate when the pectin HM content of the coatings ranges between 10.0 and 15.0% w/w (related to that of Eudragit RL) [81].

Mechanical strength can also be increased by incorporating HPMC in the film coat. Radiolabeled (99mTc) tablets coated with a 3:1:1::pectin:chitosan:HPMC films were administered orally to human volunteers. Gamma-scintigraphic studies indicated that the tablets remained intact through the stomach and small intestine. In the colon, the bacteria degraded the coat and thus the tablets disintegrated [82].

3.5 Double-coated systems

Coating core tablets with a polysaccharide film followed by an enteric coat is another means by which drug release to the colon can be guaranteed. The enteric coat protects the system from harsh gastric conditions, and as the system reaches the small intestine the enteric coat starts dissolving and exposes polysaccharide coat to the small intestine. Polysaccharide films degrade only when they reach the colon. Thus, these systems have gained high acceptability. A general method of preparation and mechanism of drug release from these systems is shown in **Figure 1**.

Tominaga *et al.* [83] prepared a colon-targeted formulation by using a double-coating system. The core, composed of acetaminophen, was coated with an inner coating layer made of chitosan and an outer coating layer made of phytin, a gastric acid-resistant material.

3.6 Compression-coated system

Compression-coated systems are the most popular tool to target drug to the colon in recent times. Although these systems require a special compression machine and personnel skills, the major advantage of this system is its versatility to deliver a wide variety of drugs. A general method of preparation and mechanism of drug release from these systems is shown in **Figure 2**.

3.6.1 *Pectin as a compression coating material*

Pectin as a compression coat was evaluated for its capability to target drug to the colon. This technique was compared with

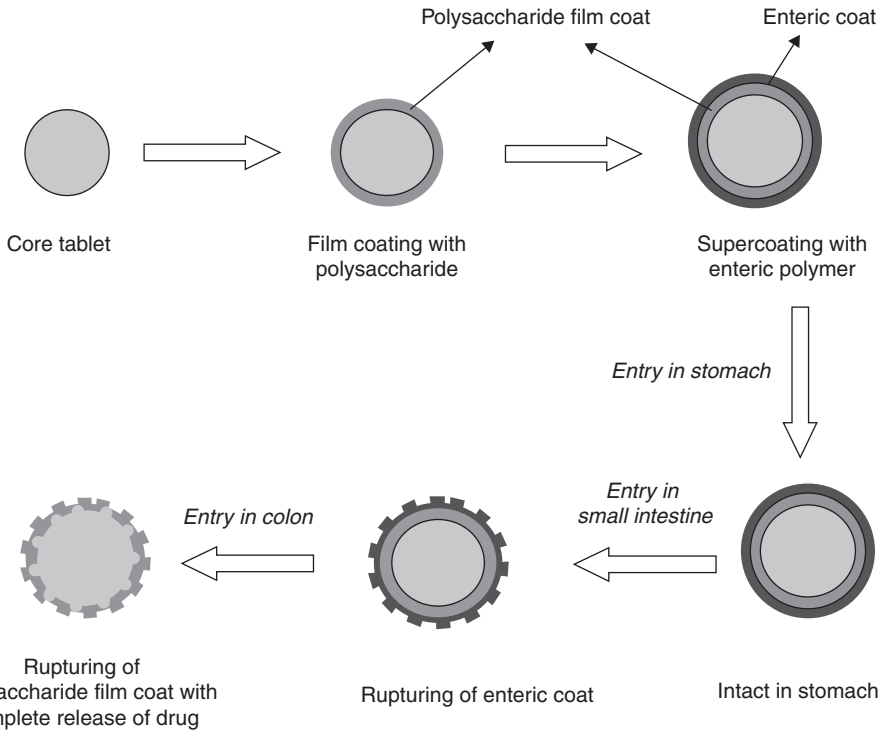


Figure 1. Colon-targeted double-coated systems.

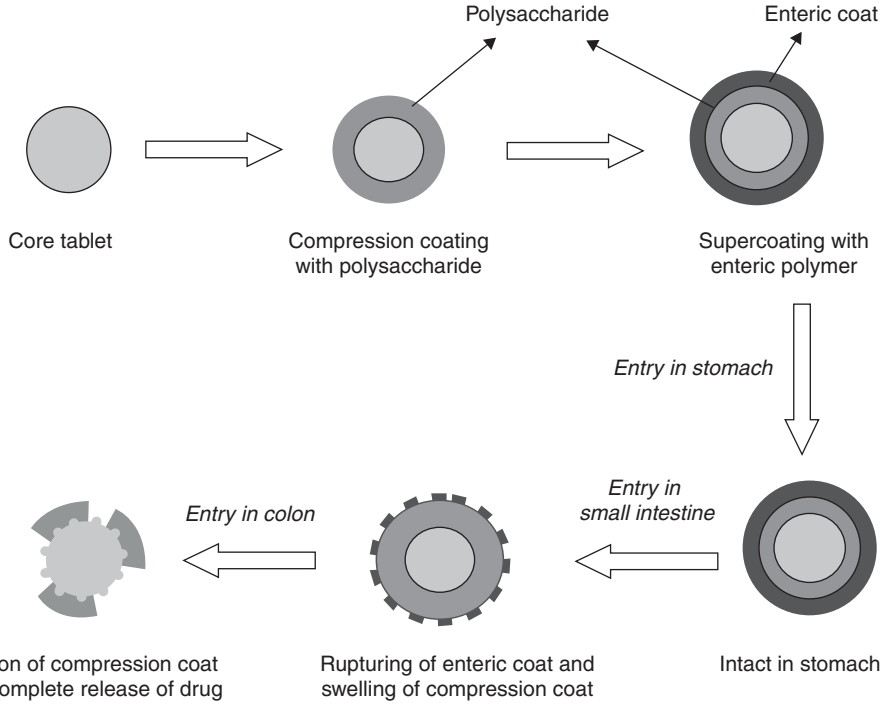


Figure 2. Colon-targeted compression-coated systems.

plain matrix tablets. Calcium pectinate-indomethacin tablets prepared by both the approaches showed no release at pH 1.5 for 2 h. At pH 7.4 plain matrix tablets showed drug leak but compression-coated tablets remained unaffected. Addition of pectinolytic enzymes increased the drug release in both cases, but compression-coated tablets released less drug (57.6 ± 2.5%) compared with matrix tablets (74.2 ± 4%) after 12 h. Thus, the compression coating technique was useful for delivery of drug to the colon [84]. Pectin-Compritol® ATO 888 was used successfully as a compression coating mixture to direct mesalamine to the colon [85].

3.6.2 Guar gum as a compression coating material

The compression coating approach was used by Krishnaiah and co-workers to direct tinidazole, ornidazole and 5-fluorouracil to the colon. *In vitro* studies revealed that tinidazole tablets compression coated with 55 or 65% guar gum, ornidazole tablets compression coated with either 65 or 75% guar gum, and 5-fluorouracil tablets compression coated with 80% of guar gum coat showed minimum release in the first 5 h, targeting maximum drug to the colon [86-88].

3.6.3 Chitosan as a compression coating material

The compression coat of mixture of spray dried chitosan acetate and HPMC in the ratio 60:40 was capable of retarding the release of 5-ASA until the dosage forms reached the colon [89]. 5-Flurouracil tablets compression coated with granulated chitosan successfully directed drug to the colon. X-ray studies confirmed localization of the system to the colon [90].

3.7 Enteric-coated hydrogels and microspheres

Most of the polysaccharide-based colon-targeted drug delivery systems developed recently use enteric coating to provide protection to the system from the acidic conditions of the stomach. Enteric-coated multi-unit systems provide the advantage of longer residence time in the colon. Multi-unit systems explored by the researchers consist mainly of hydrogel beads and microspheres. General methods for the preparation of hydrogel beads and microspheres are shown in **Figures 3** and **4**, respectively.

3.7.1 Pectin-based hydrogel beads

Calcium pectinate gel beads containing 5-fluorouracil prepared by an ionotropic gelation method were enteric coated with Eudragit®S100. *In vivo* data showed that Eudragit S100-coated calcium pectinate beads delivered most of their drug load (93.2 ± 3.67%) to the colon after 9 h [91].

3.7.2 Pectin-based microspheres

Eudragit S100-coated colon-targeted microspheres of 5-fluorouracil were prepared by an emulsion dehydration method. From the organ distribution study in albino rats, it was concluded that Eudragit-coated pectin microspheres can be efficiently used to target 5-fluorouracil to the colon [92]. Eudragit-coated pectin microspheres prepared using the solvent evaporation method showed no drug release at gastric pH, however continuous release of drug was observed from the formulation at colonic pH. Drug release was found to be higher in the presence of rat cecal content [93].

3.7.3 Chitosan-based hydrogel beads

Eudragit S100-coated chitosan beads offered a high degree of protection in the upper GIT and delivered the maximum amount of satranidazole to the colon [94].

3.7.4 Chitosan-based microspheres

Chitosan microspheres microencapsulated with Eudargit®L100 and S100 protected the formulation in acidic pH, but when it reached intestinal pH the coat started dissolving and in colonic fluid chitosan degraded in the presence of cecal matter, releasing a higher amount of drug in colon [95]. Chitosan microspheres prepared by emulsion crosslinking and coated with Eudragit S100 by the solvent evaporation technique successfully directed ondansetron to the colon [96].

3.8 New approaches

3.8.1 Osmotic technology

Microbially triggered colon-targeted osmotic pumps (MTCT-OP) were used to target budesonide to colon using chitosan as a carrier. Chitosan has a gel-forming property at acidic conditions, which was used to formulate drug suspension and produce osmotic pressure, whereas the colonic degradation property was explored to form *in situ* delivery pores for colon-specific drug release. The effects of different formulation variables, including the level of pH-regulating excipient (citric acid) and the amount of chitosan in the core, the weight gain of semipermeable membrane (cellulose acetate) and enteric coating membrane, and the level of pore former (chitosan) in the semipermeable membrane, were studied. The study concluded that osmotic technology when used in combination with the microbial degradation property of the colon could be used for developing colon-specific drug delivery [97].

3.8.2 UV-irradiated hydrogels

New biocompatible and biodegradable hydrogels were prepared by UV irradiation of aqueous solutions containing methacrylated dextran (DEX-MA) and methacrylated α,β-poly(*N*-2-hydroxyethyl)-dl-aspartamide (PHM). *In vitro* studies showed that DEX-MA/PHM hydrogels undergo negligible hydrolysis in simulated gastric and intestinal fluid in the absence of dextranase. On the contrary, when dextranases are present in the external medium, partial degradation occurs. The enzymatic biodegradability is due to the combination of DEX-MA with PHM, as crosslinked DEX-MA alone (with degree of substitution 20 mol%) does not undergo degradation by dextranase. The potential use of a DEX-MA/PHM-based hydrogel for the treatment of inflammatory bowel diseases was evaluated by loading it with beclomethasone dipropionate and evaluating the effect of dextranases on its release [98].

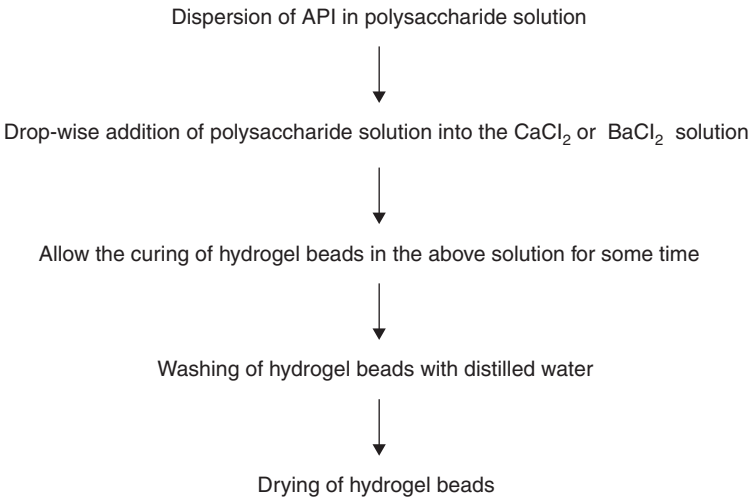


Figure 3. Method of preparation of colon-targeted hydrogel beads.
API: Active pharmaceutical ingredient.

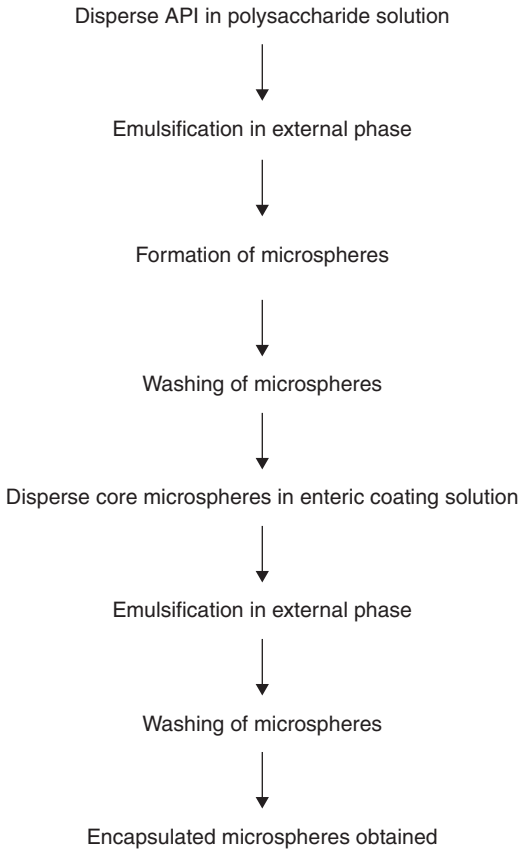


Figure 4. Method of preparation of colon-targeted microspheres.
API: Active pharmaceutical ingredient.

4. Conclusion

Various polysaccharide-based drug delivery systems along with their basic properties and method of preparation have been summarized in this article. The use of naturally occurring dietary polysaccharides as drug carriers for colonic delivery simplifies the issues of safety, toxicity and availability. Researchers may adopt any of the listed methods to target drugs to the colon, but special care in method selection is required if the process is to be scaled up. Future investigations may concentrate on the development of such polysaccharide-based systems, which have fewer processing steps and are easy to manufacture.

5. Expert opinion

There has been tremendous interest in developing colon-targeted drug delivery systems over the last decade, but only enteric-coated colonic tablets have been able to hit the market so far. The vagaries in pH of different organs of the GIT pose problems for those systems that take into consideration specific values of pH for their activation. Microflora-activated systems appear to be more promising because the abrupt increase of the bacteria population and associated enzyme activity in the colon represent a non-continuous event independent of gastrointestinal transit time.

On comparing the colon-specific drug delivery systems reported previously, the recently used approaches detailed in this review show the advantages and applications of using polysaccharide-based pharmaceutical excipients for site specificity of drug release. For any polysaccharide-based colon-specific drug delivery, the rate-limiting step for activation of the system is the ability of polysaccharides to hydrate and swell. The resultant swelling creates a diffusion barrier at the surface of the solid dosage form during its passage through the GIT. These hydrated layers of polymers allow the penetration of colonic enzymes/bacteria, which leads to degradation of the polysaccharide barrier, hence releasing the drug at the target site. For those systems where polysaccharide fails to swell, its subsequent degradation is stalled, which in turn hinders drug release at the target site. This can be considered a major setback for using pure polysaccharide-based systems.

In this review different combinations of polysaccharides with different synthetic polymers have been classified exhaustively. The three best approaches that can guarantee drug delivery to the colon are: mixed film coatings; double-coated systems; and compression-coated systems. In all these approaches, synthetic polymers such as ethylcellulose, HPMC or an enteric polymer are either added to a polysaccharide coat or applied as a separate barrier coat. Researchers have shown promising results using these approaches. The only challenge ahead is to scale-up the process at the commercial level.

A big area of concern is to develop multiple unit colon-targeted systems. So far, a large amount of work has focused on developing single unit systems for acute therapy of colonic disorders. As colonic disorders such as ulcerative colitis and Crohn's disease require chronic therapy, multiple unit system such as minitablets, hydrogel beads, microspheres and nanoparticles can be explored more frequently to provide controlled-release colon-specific drug delivery systems.

The challenges in the future will be to find a polysaccharide from which one might be able to obtain a non-permeable film or coating that also possess a high colon-specific degradability. Probably, polysaccharides with a large number of derivatizable groups, a wide range of molecular mass, varying chemical composition and above all that are stable, safe and biodegradable, may offer a correct solution.

To develop a successful market product for colonic drug delivery, the formulator needs to address the following issues before taking these systems to clinical phase trials. Is the replacement of old technologies and old drugs with complicated developments justifiable medically and economically? Is it pharmacologically not possible to cure the ailment with systemic administration of drug? Is this process/technology scalable.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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