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Bioresponsive drug delivery systems in intestinal inflammation: State-of-the-art and future perspectives☆

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ABSTRACT

Oral colon-specific delivery systems emerged as the main therapeutic cargos by making a significant impact in the field of modern medicine for local drug delivery in intestinal inflammation. The site-specific delivery of therapeutics (aminosalicylates, glucocorticoids, biologics) to the ulcerative mucus tissue can provide prominent advantages in mucosal healing (MH). Attaining gut mucosal healing and anti-fibrosis are main treatment outcomes in inflammatory bowel disease (IBD). The pharmaceutical strategies that are commonly used to achieve a colon-specific drug delivery system include time, pH-dependent polymer coating, prodrug, colonic microbiota-activated delivery systems and a combination of these approaches. Amongst the different approaches reported, the use of biodegradable polysaccharide coated systems holds great promise in delivering drugs to the ulcerative regions. The present review focuses on major physiological gastro-intestinal tract challenges involved in altering the pharmacokinetics of delivery systems, pathophysiology of MH and fibrosis, reported drug-polysaccharide cargos and focusing on conventional to advanced disease responsive delivery strategies, highlighting their limitations and future perspectives in intestinal inflammation therapy.

Contents

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1. Introduction

Colon-specific drug delivery has gained interest in recent years to deliver therapeutics (drugs, proteins, peptides) locally in numerous colonic diseases such as Crohn's disease (CD) and ulcerative colitis (UC), diverticulosis, irritable bowel syndrome (IBS), local bacterial infections, polyp, fistula, intestinal epithelial wound healing and colorectal cancer [1–3]. The etiology of inflammatory bowel disease (IBD) is characterized by persistent episodes of diffuse gut mucosal inflammation, epithelial wounds or erosions, ulcerations and bowel wall fibrosis with strictures [4]. Destruction of the integrity of the mucosal epithelial barrier is spotted in IBD condition. Severe tissue damage requires an efficient mucosal wound healing for effective IBD therapy. The aim of the current therapies is to induce and maintain remission, avoid disease progression with aminosalicylates (mild to moderate IBD), corticosteroids and biological drugs (moderate to severe IBD). These medications are administered either orally (enteric coated pills, tablets, capsules) or by parenteral (intravenous, subcutaneous injections) or rectal (enemas, suppositories, foams) delivery.

Oral preparations that provide a localized gastrointestinal (GI) effect are favoured in drug delivery design for gut mucosal healing. Oral dosage forms are the most desirable delivery route because they are more convenient and allow for a greater degree of flexibility in their formulation design, improved patient compliance with safe administration [5]. For controlled oral colon-specific release systems, the physiology of the gastrointestinal tract (GIT) allows the design of miscellaneous dosage forms over other delivery routes. The different anatomical, physiological properties of the GIT segments, transit time, pH of the gastric fluids, gut microbiota, difference in absorption and release kinetics are helpful in designing apposite disease-specific or region-specific delivery systems [6].

In general, a targeted delivery system to gut inflammatory regions is not intended to release the drug in the upper gastric tract (stomach) but release the payload at IBD site. In addition, the delivery cargo should also have a triggering mechanism that can respond to physiological changes in the GI. The GIT undergoes dynamic changes in motility, fluid content, enzymatic activity and an increase in pH from the stomach (pH 1.5) to the intestine (pH 6.5–7.5) [7, 8]. Therefore, it appears that oral colon targeted dosage forms such as time-based [9–12], pH-dependent [13–18], prodrug approach [19–21] and polysaccharide-based (microbiota triggered) colonic drug delivery [22–27] with an appropriate release pattern, disease specificity for IBD therapy.

It has been reported that the pH-dependent enteric coating systems, time-dependent systems lack in their targetable delivery because of the vigorous changes in pH (feed/fast state condition, healthy *vs* disease conditions), variations in gastric emptying, altered kinetics of the delivery system *etc*. Amongst all of the aforesaid systems (pH, time-dependent, pro-drug, microbiota triggered, *etc.*), the microbiota-activated delivery systems have been found to be the most effective delivery systems [28–30]. The basic mechanism in microbiota-triggered delivery systems is a series of coated/conjugated polysaccharides that undergo enzymatic degradation in the intestine and are largely metabolized by colonic bacteria, which further triggers the release of the payload from the delivery system at colon regions [29, 30].

The rationale of this review is to summarize the strategies developed in the past and present those that are used in IBD. Here, we have discussed briefly the potential gut physiological factors altering drug targetability, mucosal healing mechanism towards intestinal barrier repair in IBD. In addition, we have compiled the details of various polysaccharide-based systems used for colon specific drug delivery, their chemical conjugation, specific microbiota/prodrug degradation mechanisms, and merits and demerits of various reported approaches by emphasizing next generation disease responsive (biophysical, ligand based, nano/micro carrier) systems. This will enable us to point out possible advanced projections of disease responsiveness in the area of gut inflammation and wound healing. Fig. 1 has highlighted general physiological considerations of various segments of gastric tract for local drug delivery at the inflammation site [30–36].

2. Potential gut physiological factors altering drug targetability in IBD

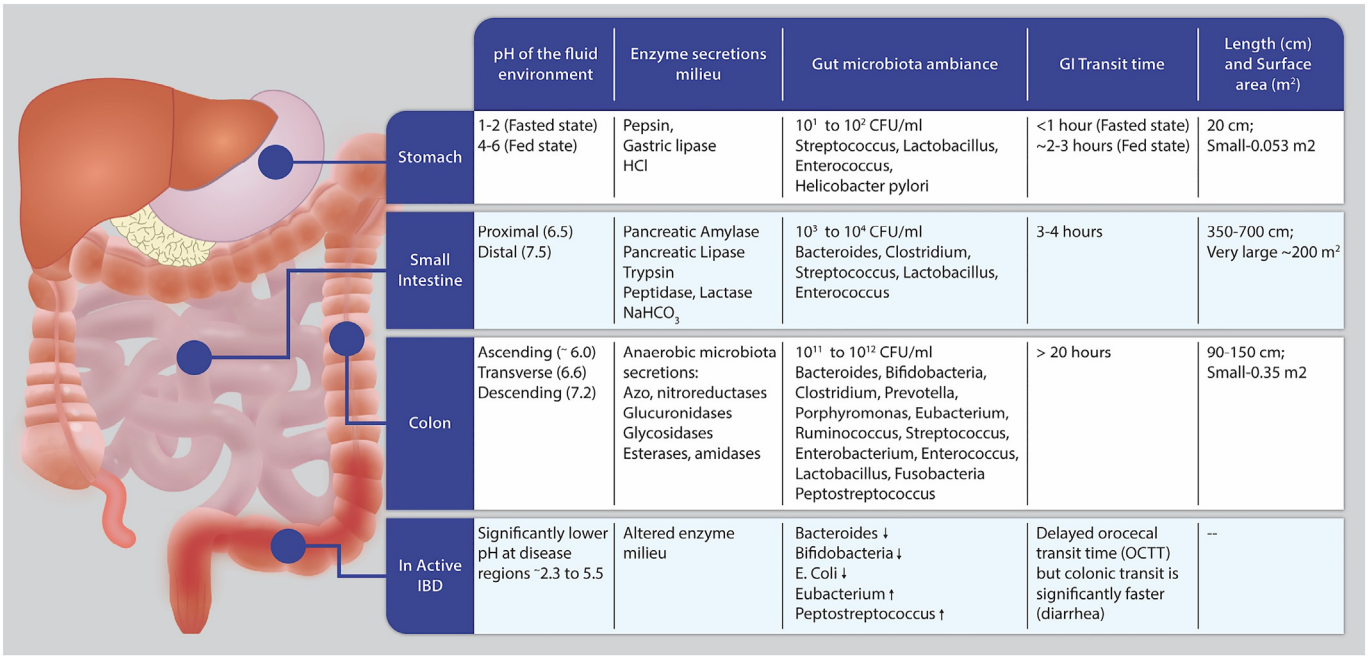
There are numerous GI physiological factors that an oral drug delivery system to IBD site relies on to get to the site of action. The design of the formulation needs to consider transit time, pH, degradation/dissolution of the system, the volume of intestinal fluid and the amount of drug that metabolizes at the site of action through enzymatic activities. All of these involve great challenges (Fig. 2) [31–34].

2.1. Gastro-intestinal pH difference

The pH differs along the GI tract, and this can be exploited for targeting lower gastric tract areas. The pH is highly acidic (pH < 2) in the stomach, which increases to pH 5.5–7.5 in the small intestine and colon [35, 36]. However, colonic pH is significantly lower (moderately acidic) in IBD patients with mucosal inflammation and epithelial wounds [37]. On the other hand, pH changes are marginally robust, can vary between individuals and can be altered significantly by fasted *versus* fed state, disease state, water intake and microbial metabolism [38]. The pH changes in different segments of the GI is a suitable parameter to deliver therapeutics to specific regions; however, relying on the dynamic pH dependent aspect may not provide enough targetability and can affect the release of compounds from pH-dependent release coatings.

2.2. Intestinal microbiota imbalance

The intestinal microbiome milieu (over 500 bacterial species) with a specific niche plays an important role in maintaining the GI physiology and provides vast benefit to the host in the breakdown of indigestible food (especially macromolecules-fatty acids, proteins and carbohydrates). The intestinal microbiome milieu forms a barrier against invasive pathogenic bacteria and helps in the development of the intestinal immune system [29, 39]. Conversely, the GI epithelium mucosal barrier constantly undergoes wound repairing by indigenous microbiota by a process called epithelial restitution (a process of repairing the epithelial gaps). This mechanism by the resident microbiota on wound repair and restitution is still under investigation [40]. The drug intake (especially antibiotics, laxatives) and diet style can significantly alter the microbiota-enzyme secretions, which can lead to conditions such as microbial dysbiosis (changes in the microbiome composition) in IBD. Such condition can lower gut microenvironmental repair and also modify the degradation of the polysaccharide coatings, conjugates to release the therapeutics.



	pH of the fluid environment	Enzyme secretions milieu	Gut microbiota ambiance	GI Transit time	Length (cm) and Surface area (m^2)
Stomach	1-2 (Fasted state) 4-6 (Fed state)	Pepsin, Gastric lipase HCl	10^1 to 10^2 CFU/ml Streptococcus, Lactobacillus, Enterococcus, Helicobacter pylori	<1 hour (Fasted state) ~2-3 hours (Fed state)	20 cm; Small-0.053 m2
Small Intestine	Proximal (6.5) Distal (7.5)	Pancreatic Amylase Pancreatic Lipase Trypsin Peptidase, Lactase $NaHCO_3$	10^3 to 10^4 CFU/ml Bacteroides, Clostridium, Streptococcus, Lactobacillus, Enterococcus	3-4 hours	350-700 cm; Very large ~200 m^2
Colon	Ascending (~ 6.0) Transverse (6.6) Descending (7.2)	Anaerobic microbiota secretions: Azo, nitroreductases Glucuronidases Glycosidases Esterases, amidases	10^{11} to 10^{12} CFU/ml Bacteroides, Bifidobacteria, Clostridium, Prevotella, Porphyromonas, Eubacterium, Ruminococcus, Streptococcus, Enterobacterium, Enterococcus, Lactobacillus, Fusobacteria Peptostreptococcus	> 20 hours	90-150 cm; Small-0.35 m2
In Active IBD	Significantly lower pH at disease regions ~2.3 to 5.5	Altered enzyme milieu	Bacteroides ↓ Bifidobacteria ↓ E. Coli ↓ Eubacterium ↑ Peptostreptococcus ↑	Delayed orocecal transit time (OCTT) but colonic transit is significantly faster (diarrhea)	--

Fig. 1. General anatomical, physiological considerations and characteristics that exist between various segments of gastric tract and in inflamed colon region.

2.3. Gastric emptying and transit time

Oral delivery of therapeutics to the inflamed colon depends primarily on gastric emptying and bowel transit time. The two factors are to be considered while formulating nano to micro size carriers, as the dosage form transit time depends on size, shape, and compactness of the system. The normal gastric emptying takes place within 2 h and the colonic arrival occurs after 5 h [41]; smaller particles have a longer transit time than larger particles. In contrast, diarrhoea patients have shorter transit time whereas constipation patients have longer transit times. However, the gastrointestinal transit time varies from individual to individual depending on various factors such as diet, mobility, stress and disease state (especially in IBD) [42].

2.4. Multifaceted enzymatic degradation

The enormous amount of anaerobic microbiota present in the lower gastric tract gains energy by fermenting the undigested ingredients.

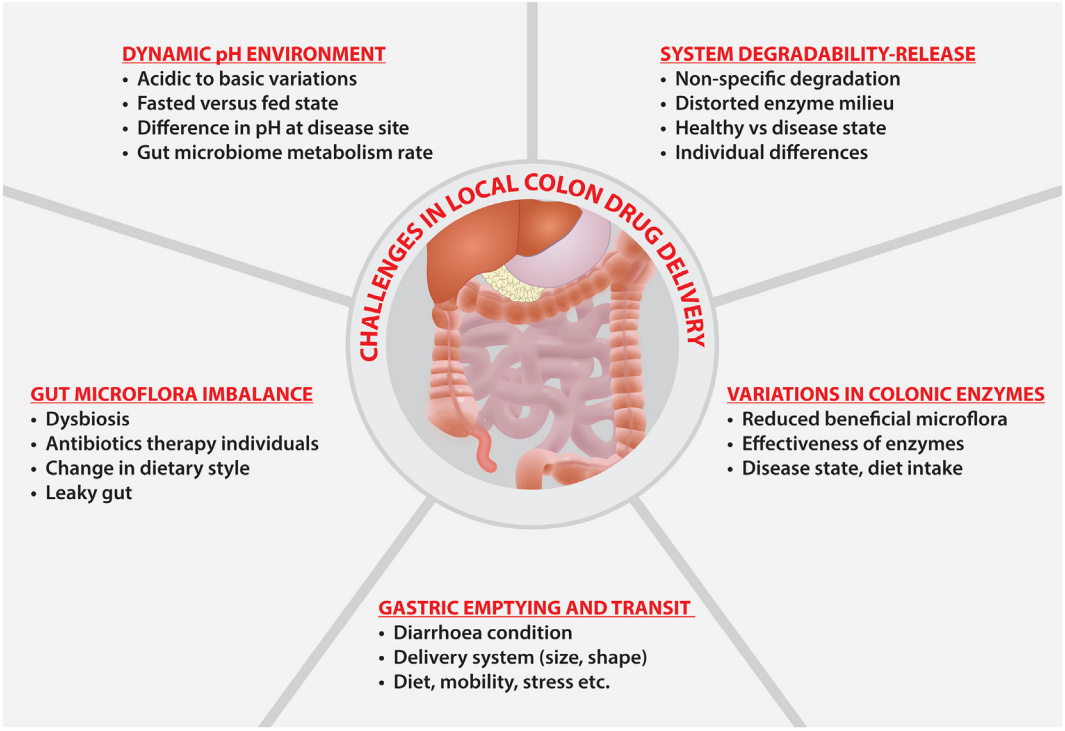


Fig. 2. Numerous dynamic, inter-related gastrointestinal physiological factors that affect the reliability of inflammation specific colon delivery systems.

Substrates such as polysaccharides/carbohydrate polymers that remain undigested in the stomach and small intestine are degraded by the anaerobic microbiota of the colon (bacteroides, bifidobacteria species and eubacteria) to smaller monosaccharides. These are used as energy sources by the bacteria [29, 43]. Production of short chain fatty acids and modification of bile acids by indigenous microbiota present in the gut helps in damaged epithelial restitution [44]. Drug carriers with polysaccharides act as prebiotics (non-digestible food ingredients which can be fermented by gastrointestinal microbiota) to the colonic bacteria and contribute to the drug release mechanism. However, the reliability of gut microbiota and their enzyme secretions depends on the disease state, diet intake and whether patients are undergoing antibiotic therapy.

2.5. Altered dissolution, degradation of the delivery systems

The drug release from a polysaccharide-based system can be controlled by a variety of mechanisms (enzymatic degradation, chemical degradation, pH-dependent degradation). The drug release mechanism of an oral gastrointestinal delivery system is mainly a dissolution control, diffusion control process. In a reservoir capsule system (encapsulation) in which the drug core is coated/conjugated by the polymer, the rate of drug release is determined by the thickness and dissolution rate of the polymer coating. In contrast, in the matrix system (the drug is distributed in a polymer matrix), the rate of release depends on the matrix degradation [7, 30, 45].

3. Wound or mucosal healing (MH) and fibrosis in intestinal inflammation

The active stages of IBD are characterized by intermittent wounding and inflammation in the affected intestinal regions. The molecular pathogenesis of IBD is not fully understood, but key contributing factors include loss of intestinal immune homeostasis, defective mucosal barrier, bacterial translocation and endotoxin secretions. Inflammation is associated with infiltration of innate immune system cells (macrophages, dendritic cells and neutrophils) and adaptive immune system cells (T-cells and B-cells), and their secreted mediators (chemokines and cytokines), which cause the disease progression [4, 46, 47].

The progress in mucosal damage and inflammation causes a decrease in transepithelial resistance at the wound site as well as at the adjacent epithelium [48]. Increased release of reactive oxygen species (ROS), metalloproteinases contributes to the induction of tissue destruction and necrosis [49, 50]. Tumor necrosis factor (TNF-α), interleukin-1β (IL-1β) and Interferon-γ (IFN-γ) associated molecular mediators are other crucial contributing factors to mucosal wounding, apoptosis and enhanced permeability at the wound site [51, 52]. Additionally, IBD patients suffer from decreased levels of integral transmembrane tight junction proteins (claudins, occludins) and junctional adhesion molecules leading to decreased barrier function and increased gut permeability to microbial endotoxins, ligands resulting in a systemic inflammatory response [48].

In response to inflammation-driven bowel damage, the intestinal epithelium vigorously self-renews the new epithelium and quickly begins to repair by clotting, granulation tissue formation (leukocytes), extracellular matrix (ECM) formation (fibroblast activation/proliferation) followed by angiogenesis (Fig. 3). Restoration of barrier function through MH has the potential to become a key treatment target in IBD. A recent finding suggests that multiple Toll-like receptors (TLRs) activation of gut myofibroblasts secretes CXC chemokine ligand 8 (CXCL8). CXCL8 was primarily considered as a neutrophil chemotactic factor, but is also involved in downstream pathways in angiogenesis and fibrosis formation [53, 54]. However, the disparity between ECM

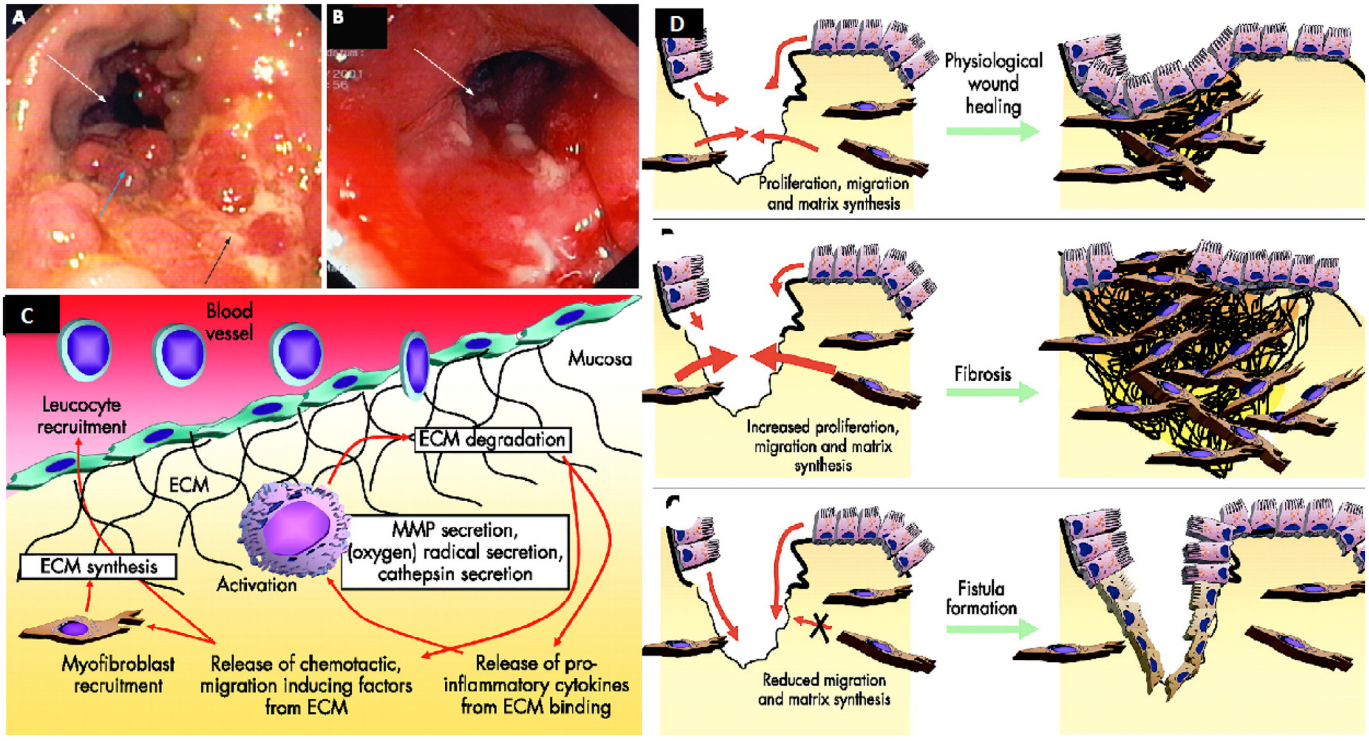


Fig. 3. Images of intestinal bowel fibrosis and inflammation (A, B): ulcerations (black arrows), fibrotic tissue formation (blue arrows) followed by narrowing of intestinal colon wall by strictures (white arrows). Schematic illustration of molecular signaling pathways involved in inflammation and ECM degradation of gut epithelium (C). Disproportional myofibroblasts activity in the healing process causing fibrosis or fistula in inflamed intestinal regions (D).
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deposition by fibroblasts and ECM degradation by recruited leukocytes leads to a fibrotic narrow intestinal wall.

The pharmacodynamics of gut wound healing and inflammation includes the first line management therapeutics such as aminosalicylates (mesalamine, Balsalazide, olsalazine, sulfasalazine, *etc.*) by pH and microbiota based delivery systems. Conversely, mesalamine *in vivo* activity on epithelial restitution and wound healing is still unresolved [55]. Patients who do not respond to aminosalicylate class drugs can be treated with corticosteroids, thiopurines (azathioprine or 6-mercaptopurine) and calcineurin inhibitors (cyclosporine and tacrolimus). In the second line management, therapeutic agents such as corticosteroids (dexamethasone, prednisone, hydrocortisone, budesonide *etc.*) are strong inhibitors of NF-kB signaling, which is essential for inhibition of cytokines; however, there is no convincing evidence of epithelial restitution/mucosal alterations [56].

The therapeutic dogma has changed from non-specific immunomodulators to biological drugs with precise anti-inflammatory activities with injectable dosage forms. TNF-α plays a key role in the stimulation of intestinal inflammation through regulating the NF-kB pathway. Infliximab, adalimumab, golimumab and certolizumab are a few TNF-α binding antibodies approved as therapeutics for mucosal healing and maintenance of moderate-to-severe IBD. Anti-integrin antibodies (vedolizumab, natalizumab) inhibit the migration of lymphocytes across the mucosal barrier by targeting the α4β7 integrins [57].

Due to the chronic nature of the IBD, development of the intestinal fibrosis is a common event. However, so far little is known about the underlying mechanism of fibrosis process and related molecular pathogenesis. Treatment of ulcerative gut with immunosuppressants, biological drugs is aimed at blocking or inhibiting the inflammatory cascade pathways at the disease site. The associated side effects of systemic delivery (intravenous/subcutaneous), and imprecise oral targetability systems are foremost therapeutic challenges in the current delivery strategies. Recent observations suggest that a combination of polysaccharide chemistry with nano/microfabrication or disease responsive systems could provide major improvement(s) in the therapeutic efficacy.

4. Drug delivery strategies reported in intestinal inflammation

By observing the diverse and dynamic environmental factors of the intestine, researchers over recent decades investigated several ideal formulations for local drug delivery in intestinal inflammation. It is widely anticipated that site-specific drug delivery to the wound/ulcer regions will increase the efficacy and decrease the side effects by providing high drug concentrations locally at the disease site and cause less systemic exposure [45, 58]. To achieve this end, researchers brought a few triggering mechanisms (such as pH, enzyme linkers, diffusion based, pro-drug, pressure controlled, osmotic controlled and electrostatic approach *etc.*) constructed within the delivery system that responds to the physiological changes, in particular to colon specificity. The conventional therapeutic strategies, which are commonly used to attain colon-specific drug delivery systems, include time-controlled, pH-sensitive polymer release system, pro-drug approach, and colonic microbiota-activated delivery systems (Fig. 4).

4.1. pH-dependent polymer coated systems

A conventional approach to target the colon is pH-dependent polymers coating on capsules/tablets/nano-micro carriers that protect the drugs in the upper gastric tract and deliver the drugs to different segments upon degradation by fluid pH. Derivatives of acrylic acids and co-polymers of methyl methacrylate (trade name - Eudragit ®, Poly

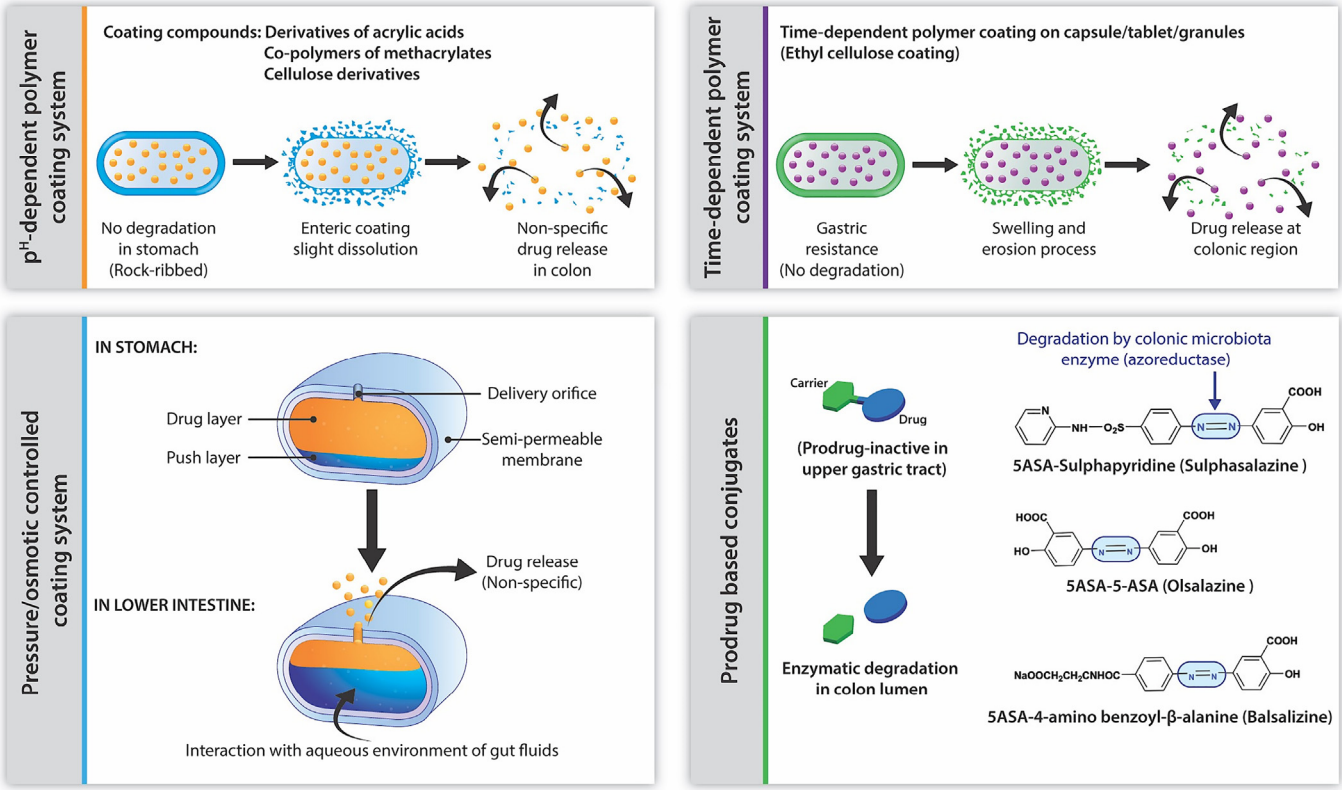


Fig. 4. Conventional delivery strategies reported for the treatment of local intestinal inflammation. Various reported delivery systems (pro-drug, pH-dependent polymer coating, time-dependent matrix system, microbiota triggering system, pressure and osmotic controlled systems) and their mechanism of degradation, release of payload in a non-specific manner in the colon region.

(methacrylic acid-*co*-ethylacrylate)), cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxyl propyl methylcellulose phthalate (HPMCP), ethyl cellulose (EC) are the most common polymers for coating tablets and capsules [28, 59]. These polymer-coated systems behave as a "rock-ribbed" system in the stomach, and degrade in a slight alkaline to alkaline colon pH environment.

Pharmaceutical formulations such as (Eudragit coated-Asacol®, Claversal®, Clipper®, Entocort®, Mesazal®, Salofac®, Salofalk® Granu-Stix) [60–63] rely on enteric coatings to target inflamed colon, and are subject to a number of variables and hence drug targeting can be less precise than desired. The commercial product Lialda® is based on MMX technology in which the drug is embedded within a lipid matrix and the phase is dispersed in a hydrogel (Eudragit S and L coated tablet system) [64]. However, one needs to consider the type of polymer selection (depending on the region-specific release), the thickness of the enteric coating, disintegration, and dissolution of the system.

4.2. Time-dependent delayed release systems

One of the other approaches by which to deliver drugs to the colon is the time-dependent release system. These systems deliver the drugs at predefined time points to a selected site of the GI tract by osmosis, swelling or combinatorial mechanism [65]. One of the earlier approaches is Time Clock®, a drug delivery system used for a time-dependent drug release of mesalamine (5-aminosalicylic acid-5ASA) to inflamed colon [9]. Pentasa® is ethyl cellulose-coated microgranules which slowly dissolve throughout the duodenum, ileum colon and release 5-ASA in colitis. A clinical trial based study suggested that Pentasa® provides an improved alternative for IBD patients *via* time-dependent drug release mechanism over that of Asacol® therapy [66, 67].

Nonetheless, to overcome the limitations of single pH or time-dependent approaches, researchers proposed a dual activating approach to deliver therapeutics effectively. Some of the technologies such as Pulsincap®, Chronotopic®, Eudracol®, Chronset™ works on the principle of pH and time (dual) dependent systems intended for colon targeted-drug delivery [2, 68]. Recently, Naeem et al., 2015, reported nanoparticles (NPs)-based systems (Fig. 5) as a new strategy for IBD therapy because of their distinctive ability to accumulate in inflamed tissues in the colon. The system comprises pH-dependent and time-dependent polymer coating to minimize early drug release in the stomach and small intestine and target to the inflamed colonic mucosa [69].

4.3. Osmotic controlled release systems

Another attractive strategy to deliver drugs to the colon is to build an osmotic gradient pressure within the delivery system that can create hydrostatic pressure on water interaction to release loaded therapeutics. An enteric-coated polymer protects the system in the stomach; as the polymer coat degrades in the colon site, water diffuses into to core of the osmotic system through a semi-permeable membrane, thereby raising the hydrostatic pressure inside the device that presses out the payload in a controlled release manner.

Osmotic-controlled release oral delivery systems (OROS) are independent of pH and time-dependent triggering mechanisms with the zero-order release of drugs to increase the availability [70]. Pharmaceutical technologies such as OROS®-CT consist of push-pull units (bilayered-drug, osmotic push layers with semipermeable membrane); upon reaching the colon, the system allows water or gastric fluid to generate hydrostatic pressure to deliver active agents [71]. Physiological gastric parameters such as altered intestinal mobility, and water/fluid availability in conditions such as IBD limit the therapeutical benefits of osmotic drug delivery systems; however, today there are no commercially available products with this mechanism.

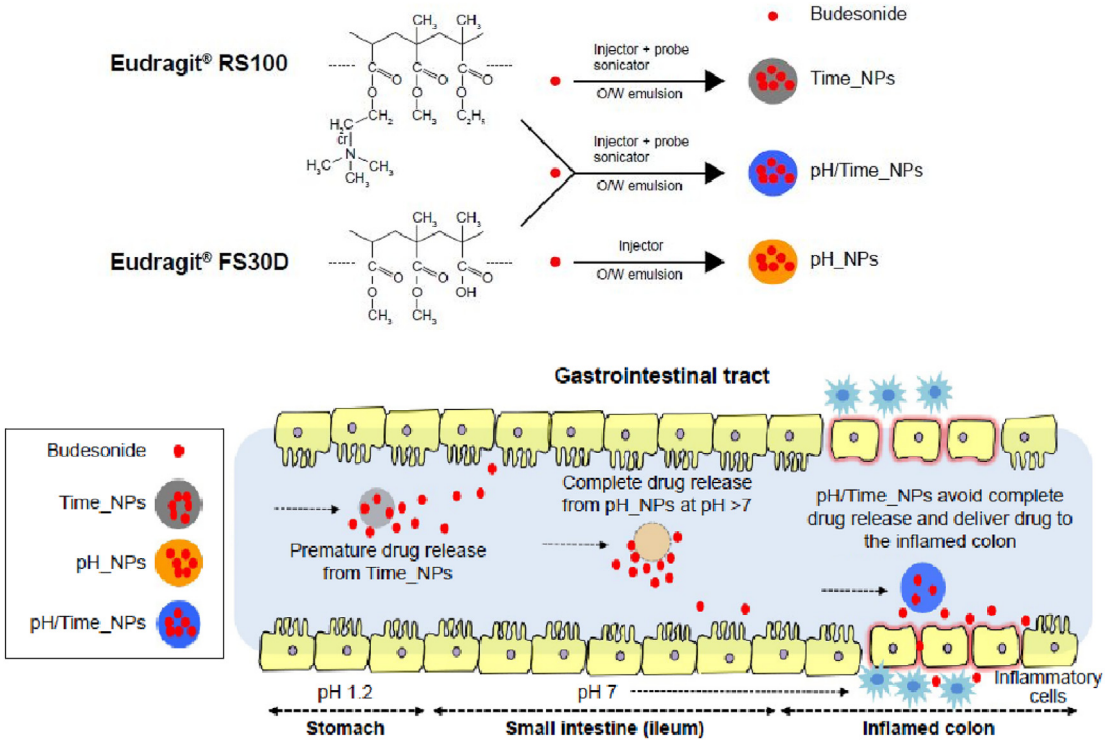


Fig. 5. Fabrication of dual responsive Eudragit coated nanoparticulate system and proposed mechanism of budesonide release; dual-system (pH/Time-NPs) has enhanced therapeutic potential in IBD when compared to the single-systems (pH-NPs and Time-NPs alone).
(Reprinted from Ref [69], with permission from Dovepress Publishing Group.)

Table 1
Source, physico-chemical, degradation properties polysaccharides used for therapeutics delivery in IBD [22–30].

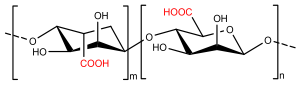
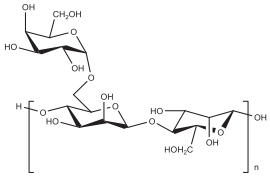
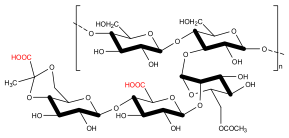
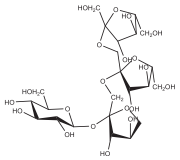
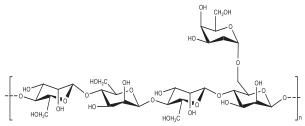
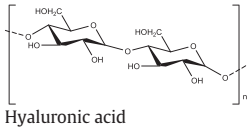
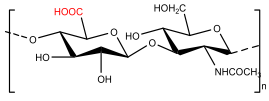
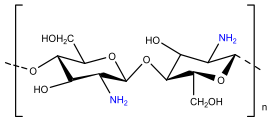
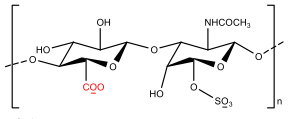
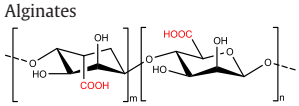
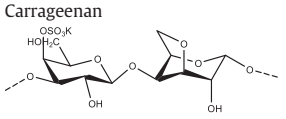
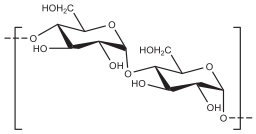
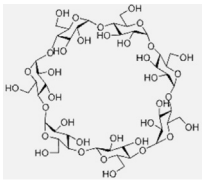
Source	Name and chemical structure	Charge and molecular chain characteristics	Solubility, hydration properties	Drug release mechanism	Degradation
Plant source	Pectin 	• Anionic (each monomer has one carboxylic acid) • Linear polysaccharide with α-(1–4)-linked D-galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues • Avg. mol. wt: 60 k–130 k g/mol	Soluble in 20 parts of water forming a colloidal, opalescent solution	Erosion and followed by pectinolytic enzymes degradation	Bacteria especially by bacteroides species
	Guar gum 	• Non-ionic, hydrocolloidal • D-Mannose monomer units joined to each other by β-(1–4) linkage in order to form the main chain with D-galactose branches attached by α-(1 → 6) bond • Avg. mol. wt: 50 k–800 k g/mol	Soluble in cold water, guar gum hydrates and swells. This gives guar gum its drug release retarding property as it forms viscous colloidal dispersions.	It has a drug release delaying property making it very useful for oral drug delivery to specific regions of colon	Bacteria (bacteroides, ruminococci, bifidobacteria)
	Xanthan gum 	• Slightly anionic • Involves cellulosic backbone, specifically β-(1,4)-D-glucopyranose glucan, with trisaccharide side chain namely (3,1)-α-D-mannopyranose-(2,1)-β-D-glucuronic acid-(4,1)-β-D-mannopyranose, on each glucose residue.	Soluble in both cold and hot water	Soluble drugs release from matrix through diffusion, insoluble drugs release by erosion.	Colonic bacterial enzymes (especially *Bacillus* sp.)
	Inulin 	• Non-ionic • (2 → 1) linked β-D-fructosyl residues (n = 2–60), usually with an (1 ↔2) α-D-glucose end group • Bacterially produced inulin • Avg. mol. wt: 0.5 kDa to 13 kDa	Inulin solubility in water is closely related to the chain length of the polymer	Alkaline pH degradation and colon specific enzymatic degradation	Bifidobacteria is the major inulin degrading microbiome in cecum
	Locust bean gum 	• Non-ionic • Main chain consists of (1 → 4) linked-β-D-mannose residues and the side chain of (1 → 6) linked-α-D-galactose. The galactose: mannose ratio is 1:4 • Avg. mol. wt: 50 to 3000 kDa	Insoluble in normal water. Heating is required for maximum solubility	Enzymatic degradation	Colonic bacterial enzymes
	Amylose 	• Non-ionic • Linear polymer of glucose linked mainly by α(1–4) bonds	Depends on amylose type. In general amylose is insoluble in water	Enzymatic degradation	Colonic bacterial enzymes (*Bifidobacterium*)
Animal source	Hyaluronic acid 	• Anionic (strongly negative charge polymer, each monomer has one carboxylic acid group) • Glucuronic acid (GlcUA) and *N*-acetyl glucosamine (GlcNAc) joined alternately by β-(1–3) and β-(1–4) glycosidic bonds • Avg. mol. wt: Oligomers to million Da	Highly soluble in water and can absorb water >1000 folds of polymer weight	Hyaluronic acid degraded by hyaluronidases and gut enzymes	Enzymatic degradation by hyaluronidases
	Chitosan 	• Cationic (each monomer has amine groups) • Linear polysaccharide consists of randomly distributed-β-(1–4) linked D-glucosamine and *N*-acetyl-D-glucosamine. • Avg. mol. wt: 50 to 190 kDa	Insoluble in water, soluble in 1% acetic acid solution.	Chitosan degrades quickly in the presence of lysozyme and colon enzymes	Colonic microbiota enzymes (glucuronidases, glycosidases *etc.*)
	Chondroitin sulfate 	• Anionic (monomer has carboxyl group as well as sulfate group) • D-Glucuronic acid linked to *N*-acetyl-D-galactosamide. Two linkages, β-(1 → 3) and β (1 → 4) are involved. • Avg. mol. wt: 18 to 150 kDa	Highly soluble in water	Degradation of the polymer by gut microbiota causes the release of the payload	Colonic enzymes (bacterial enzymes, such as "azoreductase" or chondroitin sulfatase)
Marine Source	Alginates 	• Anionic (each monomer has two carboxyl groups) • A linear copolymer consisting of β-(1 → 4) D-mannuronic acid and α-(1 → 4) L-guluronic acid residues • Avg. mol. wt: 10 to 600 kDa	Soluble in cold and hot water	Diffusion through matrix swelling and dissolution/erosion at the matrix periphery and degradation by gut bacteria	Gut Bacteria secreted enzymes (glucuronidases, glycosidases *etc.*)
	Carrageenan 	• Anionic • Polysaccharide composed of galactose and anhydrogalactose units, linked by α-(1,3) and β-(1,4) glycosidic unions. • Three types of carrageenan: kappa, iota, lambda	All carrageenan types are soluble in hot water	Delayed drug release through matrix swelling and gut enzymatic degradation	Key degradation mechanism are hydrolysis, oxidative degradation,

Table 1 (*continued*)

Source	Name and chemical structure	Charge and molecular chain characteristics	Solubility, hydration properties	Drug release mechanism	Degradation
		are used in pharmaceutical dosage forms			carrageenase enzyme hydrolysis
Microbial Source	Dextrans 	• Non-ionic • Linear chain composed of α-(1,6)-glycosidic linkage between glucose molecules while branches start from α-(1,3) linkages. • Avg. mol. wt: 3 to 2000 kDa	Highly water soluble	Dextranases cleave the dextran chain randomly and at the terminal linkages releasing the drug free into the colon	Enzymatic degradation (especially esterases and endodextranases)
	Cyclodextrins 	• Non-ionic • Cyclic oligosaccharides which consist of 6–8 glucose units	β-Cyclodextrin and γ-cyclodextrin are insoluble in water α-cyclodextrin is soluble in water	Cyclodextrins have the potential to enhance drug release from polymeric systems by increasing the concentration of diffusible species within the matrix	Colon bacteria (bacteroides)

Nevertheless, oral drug delivery *via* pH polymer coatings, time dependent, pressure controlled systems can be particularly challenging because of the variations that occur in the absorption of drugs due to associated limitations such as variability in GI transit time, irregular pH changes, uncertain efficacy, inter-patient variability and less local drug accumulation at colon site. Alternatively, researchers developed microbiota-activated delivery systems and prodrug based systems by considering the unique property of gut microbiota enzyme degradation. These systems have been found to be the most promising since the rapid increase of the gut microbiota and associated enzymatic activities in the colon signifies an alternative triggering mechanism independent of GI dynamic pH and transit time. The main principle in microbiota-activated systems (polysaccharide coating or prodrug) is that a series of polysaccharides undergo enzymatic degradation at the lower gastric tract and are predominantly metabolized by colon microbiota.

5. Polysaccharide-based systems and applications in gut inflammation therapy

5.1. Source, chemistry and properties of different polysaccharides

Substantial research is going on in the field of drug, protein and peptide targeting to lower GI by using these polysaccharide-based drug delivery systems. Polysaccharides have been extensively investigated as an approach for colon targeted drug delivery because of safety (generally regarded as safe, GRAS), non-toxic, abundant resources in nature, stability in the stomach and biodegradable. Polysaccharides, such as pectins, chitosan, hyaluronic acid, guar gum, xanthan gum, dextrans and alginates maintain stability in the stomach and degrade in the colon due to the presence of colonic enzymes. Potential polysaccharides

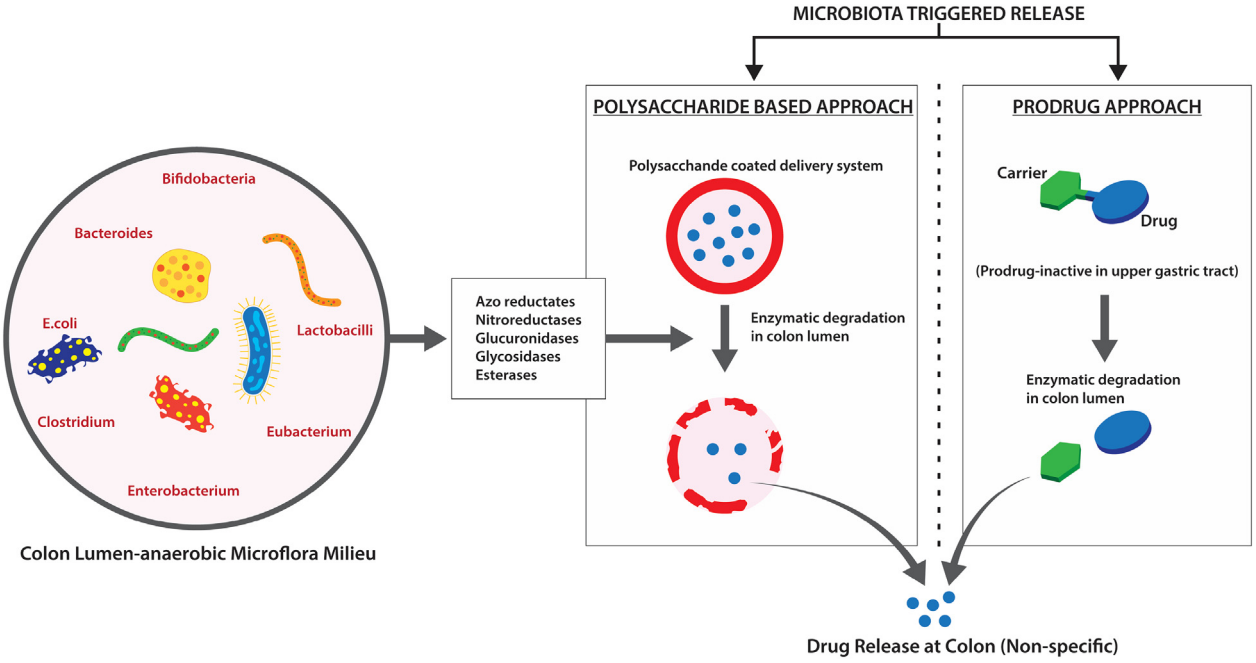


Fig. 6. Colon microbiota activated and prodrug based delivery system. Enzymatic (reduction, hydrolysis) breakdown of polysaccharide coating/conjugation by specific colonic bacteria triggers the release of loaded drugs in the colon region.

Table 2
Colon specific drug-polysaccharide based systems, dosage form, delivery system characteristics and their applications.

Polysaccharide investigated	Drug/payload molecule	Delivery system	*In vitro*/*in vivo* model used	Therapeutic application and observations	Reference
Chitosan	5-Aminosalicylic acid (5-ASA)	Chitosan capsules containing 5-ASA	Trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats	Chitosan capsules loaded with 5-ASA carriers showed better healing in TNBS-induced colitis in rat model	[78]
	Lyophilized probiotic extract (LPE)	Chitosan-coated PLGA NPs containing LPE	TNBS induced colitis in male Wistar rats	The results showed that LPE significantly repaired TNBS-induced macroscopic and histological damages and reduced neutrophilic infiltration and inflammation markers	[79]
	Bovine serum albumin (BSA)- or Prohibitin gene (PHB)	Chitosan and alginate-NPs containing BSA or PHB	Dextran sodium sulfate (DSS)-induced colitis mice	Therapeutic delivery of PHB to the colon reduces the severity of DSS-induced colitis in mice	[80]
	Nuclear factor kappa B (NF-κB) decoy oligonucleotide (ODN)	Chitosan-PLGA nanospheres	Dextran sodium sulfate (DSS) colitis model	CS-PLGA NS provides an effective means of colon-specific oral decoy ODN delivery in colitis, gene expression was inhibited in the inflamed mucosa by specifically nanoparticles uptake at inflammatory site	[81]
	Anti-inflammatory tripeptide Lys-Pro-Val (KPV)	PLA (core)-alginate-chitosan system	Dextran sodium sulfate (DSS) colitis model	Engineered nanoparticles (NPs) of Lys-Pro-Val (KPV) to the colon delivery showed enhanced therapeutic efficacy in a DSS mouse model	[82]
	Insulin	Insulin loaded chitosan capsule	Rat model	The chitosan capsules delivered the insulin at the desired location of the colon and improved systemic absorption	[83]
	Diclofenac sodium	Enteric-coated chitosan microspheres	*In vitro*	The drug was released in the desired location of the colon, and no drug release was observed in stomach	[84]
Guar gum	5-Aminosalicylic acid (5-ASA)	Guar gum and pectin tablets containing 5-ASA	Trinitrobenzene sulfonic acid (TNBS) and acetic acid-induced colitis rat model	Colon-specific formulation of 5-ASA (guar gum and pectin) was observed to be more effective in reducing inflammation in chemically induced colitis rat models when compared to colon-specific prodrug sulfasalazine as well as conventional 5-ASA administered orally	[85]
	5-Fluorouracil and Technetium-DTPA (^{99m}Tc-DTPA)	Guar gum and xanthan gum coated tablets	Human scintigraphy studies	In all the volunteers, the disintegration of the tablet was observed after 4–6 h at ascending colon/hepatic flexure, indicating *in vivo* proof of concept for colonic delivery	[86]
	Mebendazole	Guar gum matrix tablets	*In vitro*, simulated colonic fluid release studies	The optimized formulations of guar gum (20% or 30%) tablets were likely to release the drug about 83%, 50% respectively in colon but 40% of guar gum was considered unsuitable for colon targeting as the system released only 21% after 24 h	[87]
	Co-administration of 5-fluorouracil and probiotics	Guar gum and xanthan gum particles	Albino Wistar rats	This study provides the beneficial effect of co-administration of probiotics along with an anti-cancer agent in colon cancer therapy	[22]
	Piroxicam (PXM)	Guar gum microspheres	Roentgenographic studies in a rabbit model, *in vivo*	Simple, industrially viable colon-targeted, guar gum based tablets of PXM, coated with Eudragit S100 were successfully designed for the treatment of colon cancer as adjuvant therapeutic agents	[88]
Pectins	Indomethacin	Cross-linked pectin microspheres	*In vitro* drug release studies	Cross-linked pectin microspheres showed better-prolonged drug release than non-crosslinked microspheres in *in vitro* simulated buffers	[89]
	Paracetamol	Mixed film with ethylcellulose and pectin	*In vitro* conditions were simulated by changing the pH and residence time	By using a combination of ethylcellulose and pectin, the drug is protected in the upper GI tract and is released in the desired area of the colon by enzymatic breakdown	[90]
	Insulin	Calcium pectinate compression coated tablets	*In vivo* in dogs	Calcium pectinate matrices for colon specific drug delivery may be restricted to low water soluble drugs; however, in the case of water-soluble drugs such as insulin, an additional protective coat may be required	[91]
	Metronidazole	Eudragit S-100 coated pectin microspheres	*In vitro* drug release and *in vivo* biodistribution studies	Eudragit S-100 coated pectin-metronidazole microspheres can be utilized and have potential for the site specific colon delivery	[92]
	5-Aminosalicylic acid (5ASA)	Pectin coated chitosan/layered double hydroxide bio hybrid beads	*In vitro*	Pectin-chitosan/LDH-5ASA bio-nano composite beads proposed as promising candidates for the colon-targeted delivery of 5-ASA	[93]
	Metronidazole	Pectin-4-aminothiophenol (Pec-ATP) conjugate	*In vitro*	Metronidazole loaded Pec–ATP microparticles prepared by spray-drying method with improved particle stability and appropriate drug release at colon	[94]
Dextrans	Glucocorticoids (ethylprednisolone, methylprednisolone and dexamethasone)	Glucocorticoid-dextran conjugates	*In vitro* (simulated rat intestinal content based release studies)	The dextran conjugates resisted hydrolysis in upper GI tract contents but were rapidly degraded in cecal and colonic contents, indicating glucocorticoids delivery for the treatment of colitis	[95]
	5-Amino salicylic acid (5-ASA)	Dextran hydrogels	*In vitro* studies	The dextran hydrogels were not degraded in the stomach but were degraded in the cecum, which shows dextran hydrogels may make good carriers for delivery systems specific to IBD	[96]
	Hydrocortisone	Glutaraldehyde cross-linked dextran capsule	*In vitro* release studies	Without the presence of enzymes only 35% of the drug was released after 24 h. However, in the presence of dextranases, the capsule broke down rapidly and the drug was completely released	[97]
Hyaluronic acid	Oxaliplatin (L-OHP)	Hyaluronic acid-coupled chitosan nanoparticles containing L-OHP	Tumor bearing Balb/c mice	Results showed high drug concentration present in the colonic tumors with prolonged exposure time, which provides a potential for enhanced antitumor efficacy with low systematic	[98]

Table 2 (*continued*)

Polysaccharide investigated	Drug/payload molecule	Delivery system	*In vitro*/*in vivo* model used	Therapeutic application and observations	Reference
				toxicity	
	Curcumin and siCD98	HA-siCD98/CUR-NPs embedded in hydrogel (chitosan/alginate)	DSS induced mice model	Orally administered hydrogel-encapsulated HA-siCD98/CUR-NPs exhibit a better therapeutic effect against UC compared to the single drug-based formulations	[99]
	Irinotecan	Poly (ethylene glycol)-conjugated hyaluronic acid nanoparticles	Azoxymethane (AOM) induced colon cancer mice model	A theranostic system for early tumor detection and targeted tumor therapy using a model drug Irinotecan that can selectively accumulate in tumor tissue	[100]
	Doxorubicin (Dox)	Hyaluronic acid-mesoporous silica nanoparticles (MSNs)	*In vitro*	HA-MSNs loaded with doxorubicin has a much better anti-proliferative action on HCT-116 cells than free Dox or Dox encapsulated in bare MSNs	[101]
	Doxorubicin (Dox)	MSN-HA nanoparticles	*In vitro* and *in vivo*	MSN-HA/Dox nano-particles induced apoptosis in cancer cells more efficiently than free doxorubicin and inhibited tumor growth with minimal systemic toxicity *in vivo*	[102]
Alginates	5-Aminosalicylic acid	Ca-alginate-chitosan microparticles	TNBS induced colitis	Bio distribution studies of 5-ASA loaded microparticles showed high accumulation of drug at the colon site	[103]
	Icariin	Alginate-chitosan microspheres	TNBS/ethanol induced colonic mucosal injury in rats	Targeted microspheres loaded with icariin showed colon-protective effects through reducing the inflammatory response in colitis	[104]
	Hydrocortisone hemisuccinate (HCHS)	Alginate microparticles	*In vitro*	Alginate hydrogel microparticles incorporating the HCHS were produced successfully by aerosolization and homogenization methods for site specific drug delivery to the colon in the treatment of IBD	[105]
	Budesonide (BDS)	Chitosan-Ca-alginate microparticles	TNBS induced colitis in rats	The chitosan-Ca-alginate microparticles showed greater efficacy of BDS in ulcer healing	[106]
	5-Fluorouracil (5-FU)	5-Fluorouracil, in enteric shell-core alginate-based microcarrier	*In vitro*	Efficiently encapsulated 5-FU with the combination of the ultrasonic atomization and the complexation between polyelectrolytes, targeted for an effective colon cancer treatment	[107]
	Bovine serum albumin (BSA)	Alginate and aminated chitosan coated microbeads (Alg/AmCS)	*In vitro*	Amphoteric Alg/AmCS coated microbeads delivered through intestinal tract as a sensitive pH system for site-specific release of protein drugs	[108]

investigated for colon-specific drug delivery and their physico-chemical properties are enumerated in Table 1.

5.2. Microbiota triggered polysaccharide based drug delivery in active IBD

Microbiota-activated delivery systems have been found to be the most promising because of the abrupt rise of the colonic microbiota and associated enzymatic activities in the lower gastric tract. Polysaccharide-based carrier conjugates, capsule coated systems or drug-polymer matrices and prodrug systems degrade in the colon due to the presence of specific colonic anaerobic microbiota enzyme secretions that include azoreductases, nitroreductases, glucuronidases, glycosidases, esterases and amidases (Fig. 6). However, structural modifications or derivatives of polysaccharides can improve drug release, stability, bioadhesion and disease specificity [24].

Non-starch polysaccharide coatings (COLAL-PRED® system-Alizyme Therapeutics Ltd., Cambridge, UK) and similar matrix formulations depend on colon microbiota enzymatic degradation. This product has achieved successful Phase II clinical trial results and is now in phase III clinical trials for the treatment of moderate to severe ulcerative colitis [72]. The COLAL-PRED® system consists of small pellets containing prednisolone sodium metasulfobenzoate (PMSBS) with ethyl cellulose and starch derived amylose as a coating. When the system is taken orally, the polysaccharide coating protects PMSBS from stomach acidic degradation and delivers the drug locally in the colon upon enzymatic degradation [73].

Milojevic et al. reported that 5-aminosalicylic acid pellets coated with amylose: ethylcellulose in a ratio of 1:4 (w/w) have been shown to be resistant to gastric and intestinal fluids but degraded by colonic bacterial enzymes [74]. Other research, by Wilson and Basit, proved that the mesalazine-tablets coated with an amylose-ethylcellulose blend degraded by gastrointestinal bacteria to trigger mesalazine release [75]. On the starch-based system, another technology (Encode-Phloral™) contains a unique coating technology that utilizes a blend of bacteria-activated (starch) and pH-activated (Eudragit S). The pH- and bacterial-sensitive coatings can be applied to tablets and can reach the large intestine, confirming effective colon targeting with this system [24].

CODES™ technology is a combinatorial approach of pH coated and microbiota triggered delivery systems. This is designed to reduce the variability associated with time or pH-dependent drug delivery. The platform contains a class of polysaccharides (lactulose and other excipients) that are only degraded by bacteria and is coupled with a pH-sensitive polymer coating. The platform remains intact in the stomach because of the enteric protection, the coating dissolves in the small intestine (above pH 6) followed by gut bacterial degradation to release the active agent [76, 77].

The drug release from polysaccharide based-microbiota triggered systems is suitable with regard to colon specificity. However, conditions such as microbiota alterations in disease *vs* healthy conditions, enzymatic secretions, the health condition of the patient, gut infections and diet style do not guarantee the specific degradation of the microbiota triggered systems. A few colon specific polysaccharide based systems reported are enumerated in Table 2.

5.3. Prodrug based conjugates

The prodrug based approach is another strategy for drug delivery to the colon, a pharmacologically active drug is covalently conjugated to a carrier; upon enzymatic transformation, the active drug is released in a non-specific manner, *in vivo*. The conversion of prodrugs into active molecules depends upon the type of linkage. The gut microbiota secreted enzymes (azoreductase, β-galactosidase, β-xylosidase, nitroreductase, glycosidase, deaminase *etc.*) are exploited for prodrug

Table 3
Some of the reported combinatorial prodrug based conjugates for IBD treatment.

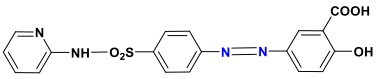
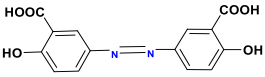
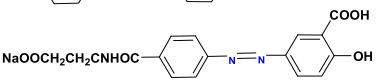
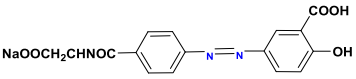
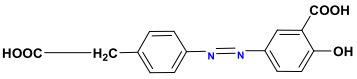
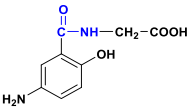
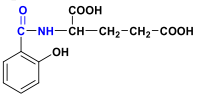
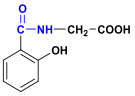
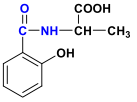
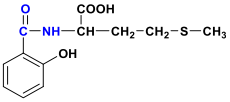
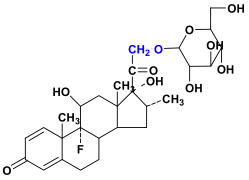
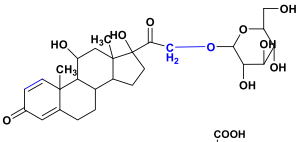
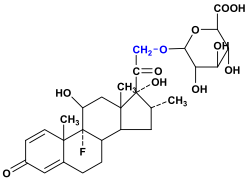
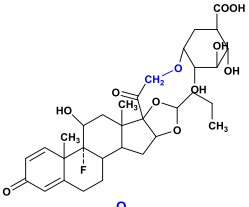
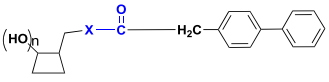
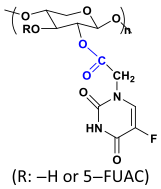
Prodrug system	Type of compound	Active drug	Carrier molecule	Chemical linkage	Ref
Azo bond conjugates	Sulfasalazine	5-ASA	Sulfapyridine		[120]
	Olsalazine	5-ASA	5-ASA		[121]
	Balsalizine	5-ASA	4-Amino benzoyl-β-alanine		[122]
	Ipsalazine	5-ASA	P-aminohippurate		[123]
	APAZA	5-ASA	(4-Amino-phenyl)-acetic acid		[124]
Amino acid conjugates	Glycine-5-ASA	5-ASA	Glycine		[125]
	Glutamic acid-salicylic acid (SA)	SA	Glutamic acid		[112]
	Glycine-SA	SA	Glycine		[126]
	Alanine-SA	SA	Alanine		[127]
	Methionine-SA	SA	Methionine		[128]
Glycoside conjugates	Glucose-dexamethasone	Dexamethasone	Glucose		[129]
	Glucose-prednisolone	Prednisolone	Glucose		[113]
Glucuronide conjugates	Dexamethasone-β-D-glucuronide	Dexamethasone	Glucuronic acid		[130]
	Budesonide-glucuronic acid	Budesonide	Glucuronic acid		[114]
Cyclodextrin conjugates	CyD-BPAA	Biphenylyl acetic acid (BPAA)	Cyclodextrin (CyD)	 (X: –NH– amide type or –O– ester type)	[131]
Acetic acid conjugates	Xyl-5-FUAC	5-Fluorouracilacetic acid (5-FUAC)	Xylan		[132]

Table 3 (*continued*)

Prodrug system	Type of compound	Active drug	Carrier molecule	Chemical linkage	Ref
				 (R: –H or 5–FUAC)	

based colon-specific drug delivery because of the degradation capability of the conjugates with such specific enzymes.

Henceforward, researchers reported miscellaneous approaches by conjugating pharmacologically active molecules to sugars, amino acids, cyclodextrins, pectins, xylans and glucuronides [109]. However, the prodrug based approach is not very adaptable because of a few drugs have appropriate functional groups to conjugate.

Amongst the reported prodrugs, the use of azo conjugates holds great promise in colon specificity. In general, azo linkages have high thermal, chemical, photochemical stability [110]. The azo compounds have been investigated as drug-carrier linkers, as a coating on drug core matrix systems that further undergo specific enzymatic metabolism (azoreductase) by lower gastric microbiota [111]. 5-ASA is the most common and effectively used anti-inflammatory drug molecule with azo conjugation for the treatment for Crohn's and colitis, few products available in the market with brand names sulfasalazine, ipsalazine, olsalazine and balsalzine under this class. In contrast, due to the presence of amine (—NH_2) group and polar nature of amino acids, they can easily conjugate with drug molecules to prepare colon-specific prodrugs to enhance the local drug availability and decrease the toxicity. Most of the non-essential amino acids like glycine, tyrosine, methionine, glutamic acid and L-alanine are conjugated with salicylic acid [112].

Glycoside conjugates are formed by conjugation of therapeutic agents with sugar moieties such as glucose, galactose and cellobiose. Immunosuppressants such as dexamethasone, hydrocortisone and prednisolone were conjugated with sugar moieties [113]. The conjugation of glucuronide with drug molecules (budesonide, dexamethasone) is one of the other approaches; this system is degraded by a specific β-glucuronidase enzyme produced by gut microbiota [114]. Cyclodextrins have been used to improve specific properties of drugs like solubility, stability, and bioavailability through additional complex formation [115–117]. They are capable of hydrolysed and slightly absorbed in passage through the stomach and small intestine and further fermented by colonic microbiota into small saccharides to release the payload [118, 119]. Table 3 shows a few reported various prodrug based conjugates for colon-specific drug delivery for IBD therapy.

6. Practical considerations, challenges and limitations of conventional delivery strategies

Current conventional drug delivery strategies are well established in the management and treatment of local colon-specific diseases. However, there are drawbacks in terms of non-specific drug release, inability to target the drug directly to the diseased tissue, high risk of systemic drug exposure and limited therapeutic efficacy. The dynamic conditions

Table 4
Comparisons of different strategies and their barriers in local gut inflammation specific delivery.

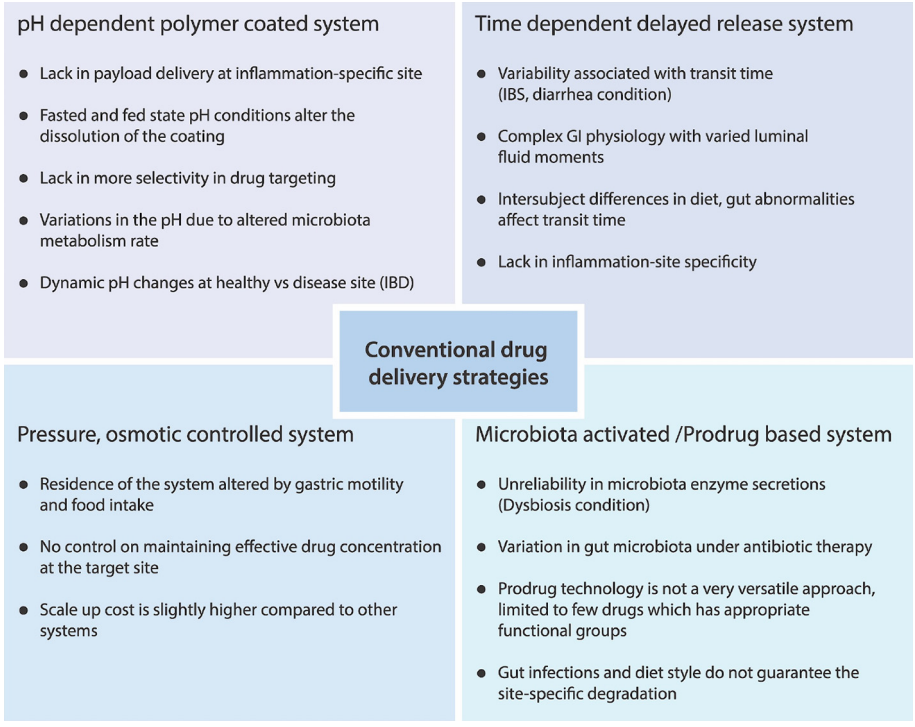


Table 5
Comparisons of different colon specific delivery strategies, challenges and limitations.

Challenges involved	pH dependent	Time dependent	Pressure, osmotic controlled	Microbiota activated (polysaccharide/prodrug)	Advanced systems (nano/microparticles, hydrogels)
Physiological challenges and limitations (oral delivery)					
Selectivity in drug targeting	+	+	+	+	+++ (achievable by surface/ligand functionalization)
Intestinal inflammation specificity	+	+	+	++	+++
Local drug availability at colon	++	++	++	++	+++
Dynamic GI pH effect	No affect	Possible	Possible	No affect	Possible
Microbiota enzymatic degradation	No affect	Possible	No affect	Possible (high)	Possible
Disease responsive delivery	+	+	+	+	+++ (by inflammation specific ligand functionalization)
Product development challenges and limitations					
Shelf-life stability	+++	+++	++	+++	+
Product scalability issues	+	+	++	+	+++
Cost	+	+	+++	+	+++
Challenges and limitations via injectable delivery					
1. Targeting drugs 100% to inflamed gut by parenteral delivery is not possible					
2. Associated systemic toxicity, especially with corticosteroids, immunosuppressant and biologic drugs					
3. Less local drug availability at colon disease site					
4. Frequent doses are required to maintain drug availability at colon					
5. Not a cost effective delivery system					
Challenges and limitations via rectal delivery					
1. Not a patient compliance route of administration					
2. Stability issues with products (suppositories, enemas and rectal foams)					
3. Can be deliver drugs effectively to rectal colitis and not effective for other forms of colitis and Crohn's					

+++ high.
++ moderate.
+ low.

of the gastric tract are still considered to be challenging in the disease responsive targetability, reliability and efficiency of the delivery systems (Table 4).

However, oral drug delivery to colon can be particularly challenging when considering the variations that occur in the absorption of drugs due to interactions with gastric secretions, membrane permeability, intestinal transit, pH variation from segment to segment and enzyme milieu. To date, comparative studies focused on the impact of different drug delivery strategies on inflammation specificity are largely absent from the literature. In the context of pH based, time dependent coating systems, these are promising in terms of preventing drug degradation in the acidic stomach environment, but lack in delivering payload at the damaged mucosal site of the colon. However changes may occur in the dynamic pH, fast/fed state, variability of transit time (IBD, IBS), fluid volume, fluid content of the GIT conditions that might change dissolution of the coating.

Systems (polysaccharide or pro-drug based) which are responsive to microbiota-derived enzymes are most promising. The colonic microbiota and associated enzyme milieu specific to lower gut, degrades the system to release drug locally with non-specific drug targetability to colitis tissue. Table 5 summarizes comparison of different colon specific delivery strategies, challenges and associated physiological and product development issues.

7. Advanced intestinal inflammation-responsive local delivery systems

Because of the limitations of non-inflammation specific conventional delivery systems, studies have been ongoing to develop advanced inflamed tissue-specific delivery systems with biophysical (charge, shape), material chemistries (surface functionalization/disease specific ligand attachment) approaches. To overcome the limitations associated with conventional approaches (pH, time, microbiota, prodrug based), researchers focused on developing different delivery systems that deliver the drugs by the use of pathophysiological parameters that are directly related to the site of disease. However, these disease responsive systems have yet to enter clinical use. The ongoing approaches (by considering inflammation pathophysiology and by the combination of polymer chemistry, nanotechnology, functionalization/conjugation) for targeted drug delivery involves improvement in the delivery system to disease areas of the lower intestine. In local colon delivery, there is presently considerable focus on micro to nanoparticulate (polymeric, lipid carriers, hydrogels) systems [133–135], charge based (electrostatic approach) systems [136–138], muco/bio-adhesive systems [139–141], and systems with surface receptor/ligand functionalization [142, 143]. Nano or microparticle properties such as size, shape and surface charge of the carrier system influence adhesion/targetability to inflamed intestinal tissue. Other physicochemical parameters of nano/micro delivery systems have yet to be explored.

Recently, an advanced disease-responsive (biophysical aspect with surface charge based) approach by Zhang et al., reported that drug-loaded inflammation-targeted (IT-hydrogel) enema microfibers administered to colitis mice has shown more therapeutic efficacy with less systemic drug exposure. The IT-hydrogel described here is made from a simple, cost-effective, nontoxic compound with long-term stability which enables sustained drug release over several days. The *in vitro, ex vivo* data strongly suggested that charge is the primary factor mediating adhesion of IT-hydrogel to the inflamed epithelial surface (Fig. 7). Overall, IT-hydrogel fibers (anionic charge) preferentially adhere to the inflamed mucosa (cationic charge) in murine colitis, and to biopsy specimens from human healthy *vs* colitis patients [138]. In terms of targetability, this approach is more consistent than conventional drug delivery strategies. Nevertheless, the system is administered only *via* rectal delivery as an enema dosage form due to system instability in the upper gastro-intestinal tract (*i.e.* stomach and small intestine). However, there is a potential for electrostatic interactions and in some cases non-specific binding of these systems with other charge-modifying substances in the colon. The design of a system solely based on surface charge seems unlikely meaning that additional strategies would be needed for local delivery of the drug specifically to diseased colonic tissue (colitis).

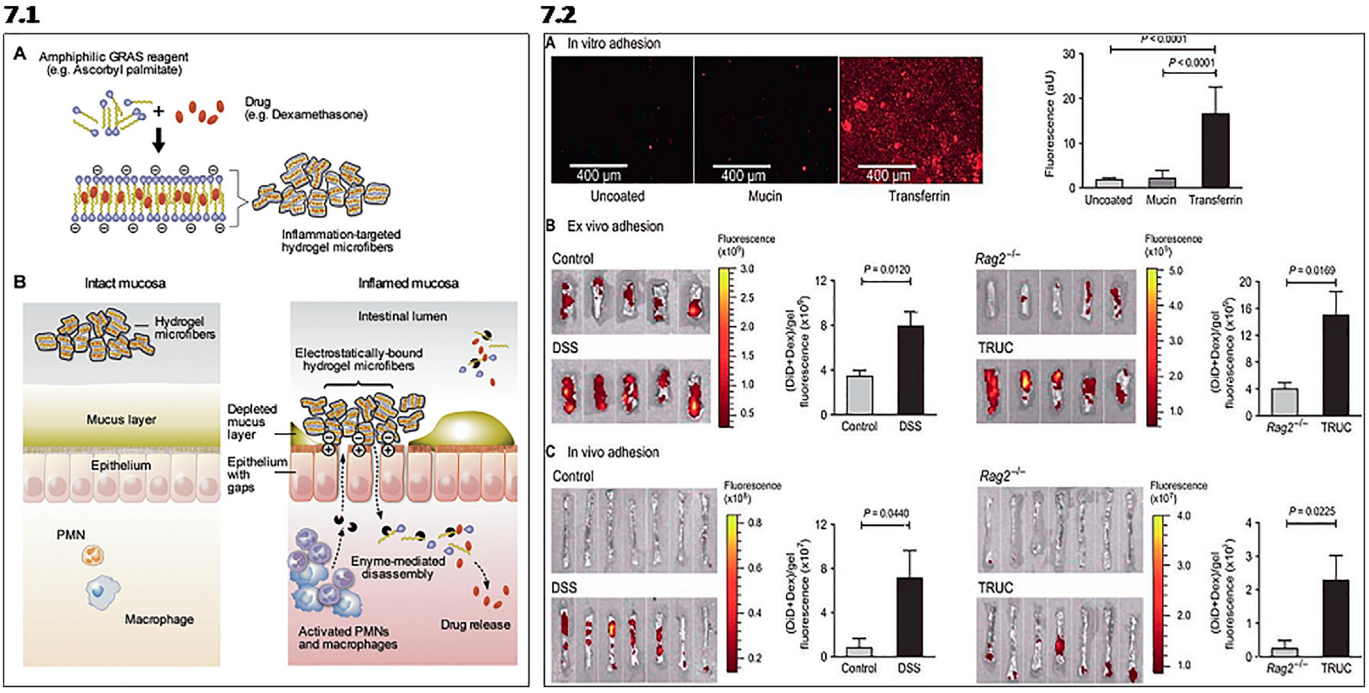


Fig. 7. Model drug dexamethasone loaded ascorbyl palmitate anionic hydrogel microfibers can specifically adhere to inflamed tissue due to ionic interaction by harnessing cationic nature of inflamed tissue (7.1). Higher fluorescence signal (7.6-fold increase) observed from the (DiD + Dex)/gel on transferrin coated plate over that of mucin-coated or uncoated plates, *in vitro*; Similarly, increased microfibers adhesion was observed in an *ex vivo, in vivo* colitis models (7.2).
(Reprinted from Ref [138], with permission from American Association for the Advancement of Science.)

Mucins within the gastric tract are negatively charged due to the substitution of their carbohydrates by sulfate and sialic acid residues [144]. Targeting the mucosa promotes improved contact with the mucosal surface for cellular uptake and release of the drug. Lautenschläger et al. [28] assessed the potential of non-functionalized (PLGA), functionalized chitosan, functionalized PEG-coated nano and microparticles of their *ex vivo* targeting ability to the human intestinal mucosa (Fig. 8).

Chitosan-functionalized PLGA nanoparticles were able to adhere to the tissue surface. However, they were unable to translocate and deposit themselves in the inflamed tissue (6.2% ± 2.6%) and healthy tissue (5.3% ± 2.3%). The strong electrostatic interaction of the positively charged particles with the negatively charged mucosa may have prevented particle translocation into the tissue. PEG-functionalized particles have shown more inflamed tissue targetability than that of non-functionalized particles. Moreover, PEG-functionalized microparticles

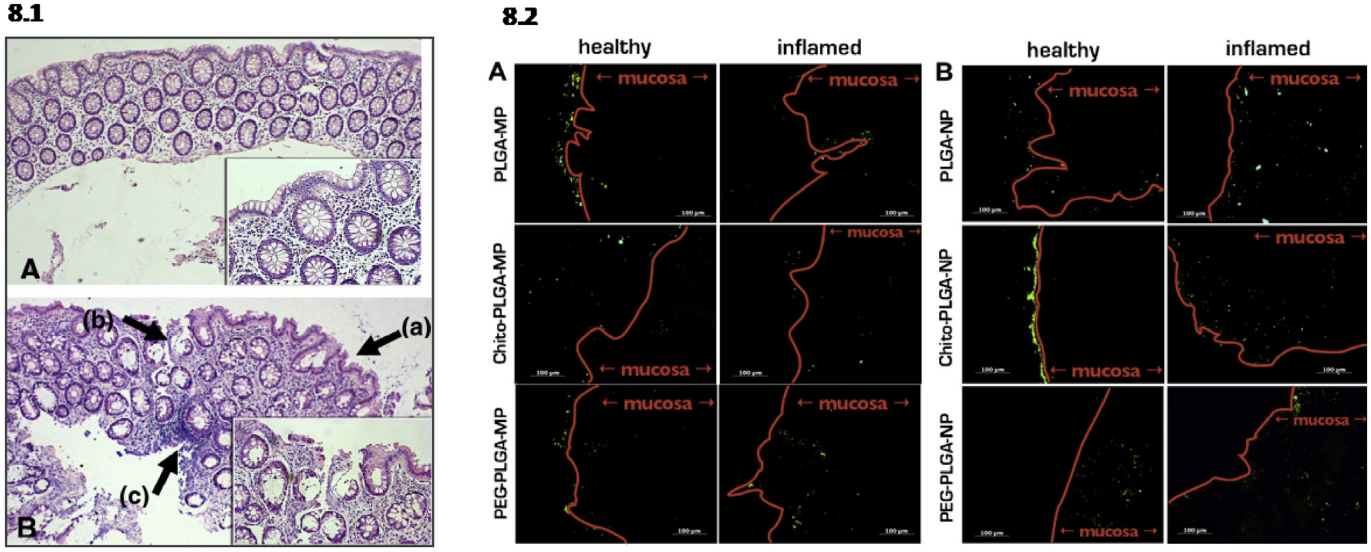


Fig. 8. Illustrative histological images of human intestinal biopsies (8.1) (non-inflamed-A; mild to moderate inflamed biopsies-B). Deposition and translocation of different particles on mucosal biopsies images after Ussing chamber experiments (8.2) (green = microparticles/nanoparticles; red = tissue border between luminal and mucosal area).
(Reprinted from Ref [145], with permission from Elsevier.)

showed a significantly increased translocation through the inflamed mucosa (3.33%) than the healthy mucosa (0.55%). This approach may be more useful for drugs that act extracellularly or only act after uptake into immune cells in active inflammation [37, 145].

The majority of the recent disease-specific targetability approaches uses ligand functionalization that is attracted to specific surface receptors, proteins and adhesion molecules at the disease site. Ligands can be coupled to the surface of nano or microparticles to improve system targeting that may increase the therapeutic effect and, in doing so, reduce the risk of side effects by improving the selective drug accumulation at the disease site. Active targeting-based nano-delivery systems have been extensively studied for colon-specific delivery *via* the oral/parenteral administration route to target cancer, local colon infection and inflammation [146–149].

Disease-specific approaches are promising in targetability, local drug availability and uptake by cells to attain more therapeutic efficacy. However, oral administration of these systems encounters challenges from acidic and enzymatic degradation; parenteral administration is still deficient in local colon-specific drug delivery with associated systemic side effects. Therefore, advanced disease-specific nano or micro delivery systems require further design and thorough *in vivo* studies to aim for clinical and translational studies, and these processes remain challenging.

Based on the current therapeutic explorations and advances in understanding the pathophysiological, pharmacological mechanisms involved in IBD development, new biological drugs and cell therapies are being investigated. Stem cell therapy appears to be a promising treatment alternative. Transplanted stem cells can be allogeneic (from a donor, usually a HLA matched sibling) or autologous. The immunomodulatory capabilities of mesenchymal stem cells (MSCs), multipotent stromal cells have been explored and investigated for the treatment of IBD by modulating the immune system *via* promotion of regulatory T-cell (Treg) formation [150, 151]. A study by Melief and colleagues confirmed that MSCs promote the generation of Tregs directly by the constitutive production of TGF-β1 and indirectly by influencing the differentiation of monocytes towards CCL18-producing type 2 macrophages [152]. Use of hematopoietic stem cells (HSCs) for severe Crohn's [153, 154], amniotic fluid stem cells (AFSCs) [155], and induced pluripotent stem cells (iPSCs) [156] are in clinical trials for IBD therapy; however, up to now the results are variable. Future in-depth basic research is necessary on mechanisms behind tissue repair, gut immunomodulation, cell-matrix systems, route of administration, dose and patient safety/feasibility studies.

Recent studies suggest that deregulation of the mucosal immune response to luminal antigens derived from the intestinal microflora, alterations in pro-and-anti-inflammatory cytokines in GIT causes IBD. Bhavsar MD and Amiji MM examined the potential of oral interleukin-10 (IL-10) gene therapy for the treatment of IBD by nanoparticles-in-microsphere oral system (NiMOS) containing murine IL-10-expressing plasmid DNA, and found that locally transfected IL-10 was very effective in reducing the levels of proinflammatory cytokines and chemokines (MCP-1 and MIP-1a) [157]. Recently, several groups have attempted to deliver TNF-α siRNA directly to inflammatory sites in experimental colitis models using nanocarrier systems [158, 159]. Wilson and group developed ROS responsive oral TNF-α siRNA delivery by using thioketal nanoparticles (TKNs) system. Orally dispensed TNF-α siRNA/TKN protected against DSS-induced colitis and effectively reduced TNF-α mRNA levels at lower intestinal inflammatory regions [160]. However, these systems are not likely to achieve maximal retention time in inflamed tissues, so further studies in human IBD treatment are warranted. Efforts are continuing by bioengineers, cell biologists, material chemists and formulation scientists to develop ideal systems for any biologically effective molecule local delivery that offer greater safety and efficacy in inflamed intestinal therapy.

8. Conclusion and future directions

Mucosal healing, epithelial restitution and symptom control have become vital goals to achieve remission and ultimately to stop disease progression. Nevertheless, although efforts to improve anti-inflammatory, immunomodulatory treatments for patients with IBD have been widespread, treatments for fibrosis and tissue homeostasis in IBD are still lacking. Therefore, further studies are essential to extend our understanding of the underlying the pathogenic triggers and mechanisms responsible for mucosal healing, fibrosis, and fistula formation.

Another area that demands further research is in determining ideal targeted delivery systems for effective treatment options. Targeted local drug delivery plays an important role in disease treatments associated with the colon and affords effective therapeutic responses for a prolonged period with low systemic side effects. Conventional colon drug delivery platforms such as the prodrug approach, pH-sensitive polymer coatings, microbiota-activated and enzyme-dependent release systems are characterized by a limited therapeutic efficacy and lack of inflammation or associated colon cancer tissue targetability. While designing the delivery system, one should consider the numerous physiological factors described in this review such as the dynamic pH gut environment, gastric emptying and transit, gut microbiota alterations, variations in colon enzymes and so on. Thus, improved oral to colon delivery technologies are essential to ensure optimal patient compliance and acceptance. Formulation scientists or pharmaceutical industry experts should also consider the shelf-life stability of the product, ease of scale-up, and cost-effective systems.

Recent years have seen an exponential increase in the number of studies employing polymeric nano and microparticulate, lipid-based systems and surface ligand functionalized systems. Significant progress has been made towards selective local drug delivery systems in the management of mucosal healing and inflammation. These strategies aim to improve the oral bioavailability and local drug delivery at the disease site in a specific fashion either by protecting the molecules from stomach enzymatic degradation or by improving their localization at the site and translocation of the system by disease tissue. Even though cutting-edge delivery systems have significantly advanced the future medication for colon associated disease treatments, the current medication status is still limited to conventional systems (enteric coated tablets/capsules, polymeric matrix systems). The translational gap with these technologies arises because of the numerous key challenges remaining amongst which are: nanotoxicity, immunogenicity, structural stability in transit, scale-up issues at the industrial level, limited product shelf-life stability, complex design of the delivery system, high manufacturing cost, and difficulty in reproducibility.

Outcomes from *in vivo*, clinical studies conducted on the various peptide/macromolecule technologies [161, 162] show positive results on colon-specific product development and translation into the market. However, challenges still exist with each of the technologies proposed and these needs to be addressed. Another area of future research is the development of advanced biopharmaceuticals loaded drug-eluting devices or implants, external stimuli-responsive systems [163] or targeted stem cell based therapies [164, 165] that could overcome the difficulties which cannot be addressed by the current medications. These systems deliver the payload at the local disease site for long-term therapy, and reduce frequent daily doses. In summary, successful medication on oral delivery to local gastrointestinal target requires parallel developments in material chemistry, formulation development to disease responsive capability and pathophysiological considerations for an effective local inflammation specific delivery.

Declaration of interests

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Abbreviations

MH: mucosal healing
IBD: inflammatory bowel disease
CD: Crohn's disease
UC: ulcerative colitis
IBS: irritable bowel syndrome
GI: gastrointestinal
GIT: gastrointestinal tract
TNF-α: tumor necrosis factor
IL-1β: interleukin-1β
IFN-γ: Interferon-γ
ECM: extracellular matrix
TLRs: Toll-like receptors
CXCL8: chemokine ligand 8
CAP: cellulose acetate phthalate
PVAP: polyvinyl acetate phthalate
HPMCP: hydroxyl propyl methylcellulose phthalate
EC: ethyl cellulose
NPs: nanoparticles
OROS: osmotic-controlled release oral delivery systems
PMSBS: prednisolone sodium metasulfobenzoate
5-ASA: 186-aminosalicylic acid
TNBS: trinitrobenzene sulfonic acid
LPE: lyophilized probiotic extract
BSA: bovine serum albumin
PHB: Prohibitin gene

DSS: dextran sodium sulfate
NF-κB: nuclear factor kappa B
KPV: Lys-Pro-Val
^{99m}Tc-DTPA: Technetium-DTPA
PXM: piroxicam
Pec-ATP: pectin-4-aminothiophenol
L-OHP: oxaliplatin
AOM: azoxymethane
Dox: doxorubicin
MSNs: mesoporous silica nanoparticles
HCHS: hydrocortisone hemisuccinate
BDS: budesonide
5-FU: 203-fluorouracil
Alg/AmCS: alginate and aminated chitosan coated microbeads
SA: salicylic acid
BPAA: biphenylyl acetic acid
CyD: cyclodextrin
5-FUAC: 208-fluorouracilacetic acid
ROS: reactive oxygen species