Ulcerative colitis is one of the two major forms of inflammatory bowel disease which has unforeseeable clinical course, marked by a chronic inflammation of the colon and remission of the disease. The treatment of Ulcerative colitis is managed by the administration of anti-inflammatory or immunosuppressive drugs that are ingested orally. However, the efficacy of the drug via oral route remains unclear as the release of drugs takes place in the upper gastrointestinal tract that allows inadequate amount of drug release to the colon thereby causing various adverse effects. Therefore, the advancement of disease targeted drug delivery strategies offers numerous gains over non-targeting by granting more effective therapy and diminishing the systemic adverse effect. In this review, we investigate and discuss various approaches that assist in targeting mechanism of the respective drugs to the colon for the hindrance and management of colonic ailments.

Keywords: Biodegradable polymers, colon targeted drug delivery system, delivery strategies, inflammatory bowel disease, ulcerative colitis.
developing CRC is impacted by the onset of inflammatory bowel disease (IBD) at younger age, long duration of the disease, primary sclerosing cholangitis, dysplasia, pseudopolyps and genetic modifications. Several diagnostic features, clinical data and laboratory markers are employed for the diagnostic purpose of UC that control the selection of proper treatments and for forecasting the patient’s prognosis.

Surveillance studies have shown amino-salicylates and its derivatives to be most successful for induction and maintenance therapy of UC. Use of corticosteroids and other drug have been implicated as an alternative or if the patient do not show any sort of response. However, immunomodulators and corticosteroids are not the treatment of choice due to their immediate side effects on long-term use; hence, amino-salicylates remain to be the treatment of choice. The existing formulation which is taken by mouth as a therapy has shown affirmative results in majority of the UC patients but the administered drug easily gets absorbed in the upper GI tract resulting with some drawbacks such as increased risk of the systemic adverse drug reaction, patient incompliance, difficult dosing regimens, first pass metabolism, reduced its potential of therapeutic success and complication in gastric retention time.

To maximize the efficacy and reduce the adverse effects of drugs for long-term management of ulcerative colitis, therapeutic agents may be administered via CTDDS. The use of pH-sensitive polymer, bacterial degrading coating material, biodegradable polymer matrix, time-dependent formulation, pro-drug and hydro gels are some of the approaches utilized for CTDDS. Table 1 highlights the advantages and disadvantages for CTDDS.

Choice of polymers used for achieving colonic delivery

Biodegradable polymers are used as a carrier for colon targeting due to their least toxicity, superior biocompatibility with the GI environment, degradability in specific colonic pH and site specificity due to biodegradable enzymes present in colon. Further, these polymers are grouped into (i) natural polymer and (ii) synthetic polymers, and these polymers belong to the polysaccharides and polyesters family. Table 2 is a list of the biodegradable polymers used for colon targeted drug delivery. Figure 1 represents the oral drug delivery targeting the colon.

Selective approaches and carriers used for successful colon targeting

Conventional approaches for colon targeting

Pro-drug approach

For colon specific delivery, the effectiveness of potential drugs can be improved for its pharmacodynamic and pharmacokinetic properties by developing it as a pro-drug wherein the covalent linkage between the pro-moiety and drug molecule may act as a diagnostic feature to aid in identification of pro-drugs. Pro-drugs are intended to undergo biotransformation thereby releasing the active drug molecule only in the colon.

![Figure 1](image-url) | Schematic diagram representing oral drug delivery targeting the colon.
Table 1 | Advantages and disadvantages of colon targeted drug delivery system (CTDDDS)

| Advantages                                                                 | Disadvantages                                                                 |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Avoid first pass metabolism                                               | Drug release may be insufficient                                             |
| Dosing frequency, toxicity and cost is reduced                            | Manufacturing process may be difficult                                        |
| Effects are localized in the colon                                         | Manufacturing defects may negatively affect drug action                      |
| Gastric irritation is reduced                                              | Unusual gastric physiology and colonic bacterial enzymes may decrease its bioavailability and effectiveness respectively |
| Retention time is increased                                                | Decreased stability due to non-specific drug interaction with colonic contents |
| Adverse drug interactions are minimized                                    | Require site specific dosage form for optimum activity                       |
| Lesser peptidase activity in colon allows delivery of peptides, insulin and growth hormones | Viscous colonic contents reduce the availability of drugs to absorptive membrane |
| Localized and systemic drug delivery is achievable                         |                                                                               |
| Chemical and enzymatic degradation in the upper GI tract is avoided       |                                                                               |

The activation of pro-drug may be dependent on pH, micro flora and distinct enzymes (glucuronidase, azoreductase, esterase, glycosidase, cyclodextranase, dextranase, and nitroreductase) present in the colon. Azo-containing pro-drug like olsalazine, ipsalazide, sulfasalazine and balsalazide were engineered to treat inflammatory bowel disease (IBD) by developing it to undergo biotransformation only after reaching colon.15-67

Bacterial metabolic processes like the azo compounds which is metabolized by intestinal bacteria is regarded among the most extensively studied processes. Such example is the reduction of a produg named sulfasalazine into sulfapyridine and 5-aminosalicylic acid (5-ASA) by colonic azoreductases.25-68 However, complete absorption of sulfapyridine (carrier moiety) through the colon causes adverse effects such as blood dyscrasias, hypersensitivity, hepatitis, hepatic failure, impotency, leukopenia, agranulocytosis, hemolytic anemia, cyanosis and thrombocytopenia.69 Incorporation of lipid pro-drugs which consists of a covalently bound drug and lipid moiety (steroid, fatty acid, phospholipid, triglyceride) into the metabolic pathways enables the crossing of barriers in the body easily.10,71 Covalent azo linkages between 5-amino-salicylates (5-ASA) and carrier molecules are most common pro-drugs used in IBD. Other examples include glucuronide, glycoside, amino acids, dextran, and cyclodextrin.67,72

**Polysaccharide based delivery system**

Polysaccharides that are selectively digested by the colon bacteria give additional option for colon targeting of drugs.7 Polysaccharide polymers are biodegradable polymeric carbohydrate molecules found in all living organisms. With their structures ranging from linear to highly branched structures, long chains of monosaccharide units covalently bounded together by glycosidic linkages make up the polymer.72 Animal polysaccharides include chitin and chondroitin sulphate while plant polysaccharides include cellulose, hemicellulose, starch, hyaluronic acids, guar gum and alginate.41,74 Polysaccharides are predominantly metabolized by colonic bacteria where they are broken down to simple saccharides by saccharolytic species like *Bifidobacteria* and *Bacteroides* consequently the entrapped drug is released. As denser cross linking slows down drug release, the rate of drug release may be influenced by the cross-linking density of the polymer and are considered safe for use.15,74,75 Additional advantages include large-scale availability, low cost, less toxicity and greater biocompatibility.71

Amoebiasis, IBD, ulcerative colitis, Crohn’s disease or colorectal cancer may be effectively treated with colon targeting polysaccharide-based micro/nanocarriers.76,77 Theranostics with improved therapeutic efficacy and safety is likely to be in existence with advancing polysaccharide-based nano materials with multifunctional and better controlled release systems (CRS’s).75,78 As polysaccharides like guar gum, pectin and amylase are metabolized in the presence of *Bifidobacterium*, *Lactobacillus* and *Saccharomyces*, co-administration with probiotics
| Natural Polymer | Synthetic Polymer | Description | Ref. |
|----------------|------------------|-------------|------|
| Chitosan       |                  | Natural, biodegradable, biocompatible, and non-toxic | 44   |
| Amylose        |                  | High amylose content ameliorates the encapsulation ability and lowers the dissolution rate in gastric condition | 45   |
| Pectin         |                  | Degraded by colonic bacterial enzymes. Pectin having high degrees of methoxylation can be crosslinked with calcium | 46   |
| Alginate       |                  | Cross-linking capability, pH responsive, getting ability, low degrees of methoxylation can be crosslinked with calcium | 47-48|
| Inulin         |                  | Undegraded in upper GIT due to defec enzymes, linking aglycosidic linkages in the fructose backbone, gets in the colon by dextranases enzyme that hydrolyze the aglycosidic linkages and cleavage takes place that liberates the drug | 49   |
| Guar gum       |                  | Sustained to deliver in colonic region | 50   |
| Dextran        |                  | Degraded in the colon by dextranases enzyme that hydrolyze the aglycosidic linkages and cleavage takes place that liberates the drug | 51   |
| Locust bean gum|                  | Locust bean gum combined with chitosan at the ratio 2:3 provide better colonic activity than locust bean gum alone | 52   |
| Dextran        |                  | Locust bean gum combined with chitosan at the ratio 2:3 provide better colonic activity than locust bean gum alone | 53   |
| Hyaluronic acid |                  | Acid interrupted by β(1/4) long D-glucosamine and N-acetyl-D-glucosamine units (α-D-glucose) linked through α-D (1/4) linkage | 54   |
| Cross-linked D-glucosamine and as a-galuronic acid residues | | | 55   |
| Acid interrupted by β(1/4) long D-glucosamine and N-acetyl-D-glucosamine units (α-D-glucose) linked through α-D (1/4) linkage | | | 56   |
| Xanthan gum    |                  | Used as a substrate by Bacteroides thetaiotaomicron and B. ovatus | 57   |
| Chondroitin    |                  | Drug requiring property, improve retention time, better bioavailability of poor absorbable drug, minimize local irritation and improve localization | 58   |

**Table 2: Biodegradable polymers used for colon targeted drug delivery**
may aid in restoration of normal micro flora along with their targeted release in colon.\textsuperscript{79,80}

**Ligand/receptor mediated delivery system**

During the inflammatory process, the receptors get overexposed on the cell surfaces.\textsuperscript{81,82} The ligands used in designing ligand/receptor mediated delivery system are selected by considering their functional expression profiles of the individual proteins/receptors at the target cells/organisms. Some of such ligands are antibodies, peptides, folic acid, hyaluronic acid, etc.\textsuperscript{71} Two of them are mentioned below:

**Antibodies.** Harel \textit{et al.} designed and developed anti-transferrin receptor antibody-conjugated liposomes, proving better targeting mucosal inflammation than unconjugated liposomes.\textsuperscript{83} Xiao \textit{et al.} also developed an orally delivered scCD98-functionalized siCD98 loaded nanoparticles for IBD therapy. The scCD98-functionalized nanoparticles reduce expression of this protein by colonic epithelial cells, macrophages; and exhibited a high affinity for CD98-overexpressed cells.\textsuperscript{84}

**Peptides.** Peptide includes many advantages like biocompatibility, cost-effectiveness, chemical diversity, and stimuli responsiveness, so, gained enormous concern as a potential ligand for delivery of drugs to the targeted site.\textsuperscript{85} Due to large binding interfaces with receptors, peptides exhibit higher binding affinity and specificity compared to small molecule ligands. Ren \textit{et al.} conducted an investigation on the application of synthesized 12-residue peptide (tyrosine kinase or TK) that interacts with integrin $\alpha_6\beta_1$ for the colon-specific delivery of anticancer drugs. TK peptide increases the uptake of human epithelial cell line (Caco-2) and also increase the penetration of tumorspheroids.\textsuperscript{86}

**pH-dependent delivery system**

Local drug delivery to the colon as available in majority of commercial-ized systems depend on altered pH.\textsuperscript{87} The neutral pH and prolonged transit time of colon offer various therapeutic advantages as a site of drug delivery.\textsuperscript{41} Using pH-dependent polymers such as CAT (cellulose acetate phthalate), CAP(cellulose acetate phthalates), HPMCP 50 and 55 (hydroxypropylmethyl cellulosephthalate), Eudragit L (copolymers of methacrylic acid and methacrylate), Eudragit F5, Eudragit S 100 and Eudragit P4135 F which react to the elevated pH(≥6.8), the colon-targeted drug delivery systems are designed.\textsuperscript{71,88,89} The dosage form is required to pass through altering pH environments of different anatomical regions of GI tract like stomach (pH 1.5–3.5), duodenum (pH 6), jejunum and ileum (pH 5.5–6.8), and caecum (pH 6.8–7.3) before reaching colon (pH 6.4 in ascending
colon, pH 7.0 in descending colon). Dosage forms coated with pH-dependent enteric polymers protect the drug from the acidic stomach but the coating starts to dissolve as pH moves towards alkaline in small intestine and ultimately the drug releases in the colonic pH. In diseased state, the pH and transit time can vary causing premature release or no release at all. There are however, certain problems linked with this approach. Attempts have been made to collaboratively utilized pH-dependent systems with enzyme-triggered systems and time-dependent systems. Fahima et al. prepared prednisolone loaded microsphere by combining pH and time – dependent polymers (Eudragit® S-100 (ES100) and ethyl cellulose (EC)) for colon targeting delivery system then evaluated and reported that the selected microsphere is able to deliver the drug to the colon thereby preventing the release of drug in the upper GIT. Akhgari et al. prepared and evaluated indomethacin pellets loaded with the combination of pH-dependent and time-dependent polymers for colonic delivery and revealed that it is effective and desirable for sustained drug release in the colonic region.

**Time release system**

Drug delivery systems that are time dependent are based on the principle that drug release is prevented until it reaches the colon. The transit time of GIT influences the site of preliminary drug release in case of time-dependent systems. Under normal physiological environment, the average transit time ranges from 2–6 hours. The transit time is shortened in IBD patients due to pathophysiological alterations. In IBD, diarrhea affects the transit time as peristaltic movement is accelerated leading to inaccurate prediction for the arrival time of the dosage form to the colon and may even lead to poor dosage availability. The colonic transit time in ulcerative colitis is 9.5–39.1 hours whereas in healthy individuals, it ranges from 41.1–62.3 hours.

Knowledge on the dosage and gastric transit time is a prerequisite for successfully drug delivery. For non-disintegrating single dosage form, the gastric emptying time ranges from 15 to 180 minutes. For small intestine, it varies lies between 3–4 hours. The average transit time in the colon for women and men is 47 hours and 33 hours respectively. Overcoming the large variation observed in gastric emptying is achieved by enteric coating in most of these systems. To improve the efficacy and accuracy of drug release, time dependent system is coupled with pH-dependent drug release and time controlled drug release.

For colon-targeted drug delivery, a promising

![Figure 2](image-url) | Process flow diagram of OROS-CT colon targeted drug delivery system.
controlled release carrier was formulated by El-Gibaly et al. Zn pectinate gel (ZPG) microparticles was loaded with ketoprofen in addition with pectinate microparticles (2–3% w/v pectin, 2.75% w/v Zn(CH3COO)2 and 2.5% w/v drug). Extended release of drug from ZPG microparticles was observed and was also concluded that the release of ketoprofen was prolonged by the formulated ZPG microparticles which simulates intestinal fluid (pH 7.4). 97

**Novel approaches for colon targeting**

**Osmotic controlled delivery system**

OROS is a novel delivery system for pharmaceuticals where release of drug occurs as osmotic pressure, which is produced upon the entry of the solvent. 98 Elementary osmotic pump and push-pull osmotic systems are two OROSs with successful delivery requiring the application of solutes such as osmogens or osmagents apart from the drug. Additionally, osmotically active salt like NaCl, KCl, etc. maybe combined with the drug. 99 OROS-CT or OROS capsules may consist of a single osmotic agent or may contain up to five or six push pull osmotic unit. 102

The gelatin capsule containing the push-pull units dissolves immediately after the OROSCT is swallowed. However, the impermeable enteric coating prevents the absorption of water in the acidic environment of the stomach thereby preventing delivery of drug. The coating (Eudragit S 100) dissolves with increasing pH environment (pH >7) in the small intestine and with the entry of water, the osmotic push compartment swells and a flowable gel is formed in the drug compartment. 100 The gel is then forced out through the orifice and the rate of release is precisely controlled via the semi-permeable membrane depending on the rate of water transport. For treating UC prevention of premature drug delivery is assured by designing each push pull unit to obtain a 3–4 hour post gastric delay so that release of drug starts only when a unit arrive at the colon. A constant release rate of the drug for as long as 24 hours can be maintained by OROS-CT units in the colon otherwise can deliver the drug within a period of just four hours. 38 Figure 2 represent the flow diagram of OROS-CT colon targeted drug delivery system.

**Pressure controlled system**

Pressure-controlled colonic delivery capsules (PCDCs) is a novel technique which has overcome limitations of different basic techniques like produgs, pH, time-dependent systems and microbial triggered delivery system by enhancing site specificity and feasibility of production. 101 Human studies reveal that by the use of magnetoscintrigraphy, PCDCs are able to deliver drug to the colon. 102 PCDS bears the luminal pressure found in small intestine but collapses in high colonic pressure. This results in drug release after 3–7 hour of oral administration. PCDS are capsule shaped suppositories coated with water insoluble polymer ethyl cellulose. 72

In PCDC, the drug dispersed in a suppository base, is coated with ethyl cellulose and hydrophobic polymer. The suppository base melts as it is swallowed and with increasing volume, the system resembles liquid-filled ethyl cellulose balloon (ECB) that is capable enough to resist the intestinal pressure resulting from peristalsis in the small intestine. 25 As water is reabsorbed from the large intestine, the luminal pressure increases due to the ongoing peristaltic motion coupled with increasing viscous contents. 97 Peristalsis induced intestinal pressure is a major factor influencing the disintegration of ECB. Hence, for PCDCs, the thickness of ethyl cellulose membrane plays a major role in delivery of drugs. 102

**Pulsatile delivery system**

Pulsatile delivery system (PDS) is effective when delivery systems like sustained delivery cannot fulfill the requirements necessary to deliver optimum quantity of the drug within specified time. 103 They are designed to deliver a drug at a controlled and predetermined rate in order to release their therapeutic agent within minimum amount of time to exert its therapeutic action instantly following programmed off release phase preventing the release of drug 3–5 hr after entering into small intestine. 98,104 Time-controlled pulsatile drug delivery systems are controlled by the system while site-specific delivery pulsatile drug delivery systems are controlled by pH or enzymes in the GIT. 105 Drug resistance, drug tolerance and the physiological
system activated due to constant drug concentration in tissues and blood are some problems associated with PDS. PDS is dependent on two methods of drug deliver, i.e. pulsincap system and port system. Pulsincap device is made up of a half capsule body (non-disintegrating) sealed at the open end along with a hydrogel plug and is enclosed with a water-soluble cap. This capsule swells as it comes in contact with a dissolution fluid and the plug pushes itself externally to the capsule causing rapid release of the drug.

Port system has a gelatin capsule coated with an insoluble plug that is housed in a semi-permeable membrane (e.g. cellulose acetate) along with the drug formulation and an osmotically active agent. A coating thickness-controlled release is achieved as the capsule and dissolution fluid comes in contact and then allowing the entry of water through the semi-permeable membrane resulting in increased pressure to expel the insoluble plug after a lag time. Another advantage for this system is that it evades the second time dosing which benefits workers and school children’s during working hours. Figure 3 and 4 represents the design of pulsincap and port system respectively.

**CODESTM technology**

CODESTM technology is a unique CDDS designed to steer clear of the innate difficulty related with time dependent systems or pH in terms of attaining feasibility of manufacturing process and in-vivo site specificity. Microbial-triggered CDDS and pH-dependent approach results in CODES whose mechanism involves lactulose wherein it facilitates site specific drug release in the colon by acting as the trigger. The system essentially consists of a tri-layered coated tablet with core drug and biodegradable polysaccharides. The tablet core is coated with an acid soluble polymer, viz. Eudragit E. This is further coated with polysaccharide such as lactulose and subsequently coated with an enteric polymer Eudragit L. Eudragit L protects the tablet from gastric enzymes and immediately dissolves after gastric emptying. Enteric coating protects the CODES below pH 6. But upon entry into the colon where pH is

**Figure 4** | Schematic design of port system.

**Figure 5** | Conceptual design of CODESTM technology.
above pH 6, the polysaccharide inside the core diffuses out through the coating and gets metabolized by bacterial enzymes into organic acids which in turn lowers the pH to dissolve the produced Eudragit E thereby releasing the drug.\textsuperscript{25,72,107} Figure 5 represents the design of CODES™ technology.

**Multi-particulate system**

Oral dosage forms consist of multiple small discrete units known as multi-particulate drug delivery systems.\textsuperscript{37} They usually consist of thousands of sphere-shaped particles with a diameter of 0.05-2.00 mm.\textsuperscript{107} Multi-particulate systems are known for controlled, sustained oral drug release with better chances of local targeting and increased stability in GI conditions due to encapsulation. Particulate delivery systems show higher adhesion at the site of inflammation due to increased mucus production, enhanced permeability due to disease state and particle uptake due to a number of immune cells. This phenomenon is found to be size dependent.\textsuperscript{72} Due to their small size, uniform and safer drug absorption is observed as there is rapid distribution throughout the GIT. Residence time of particles in large intestine is associated with reduced particle size which may benefit patients with diarrhea.\textsuperscript{106} Advantages include dosage strength flexibility, optimized release for a single drug and drug combinations with minimizing food effect, exhibiting poor solubility in lower intestinal pH, and attainment of required pharmacokinetic profile with pH above 8.0.\textsuperscript{106}

Due to less inter subject variations, a single layered or multi-layered multi-particulate drug delivery systems has a great reproducible drug release pattern for the inflamed sites in the colon\textsuperscript{88} Pellets, beads, granules, nanoparticles and micro particles are the type of formulations included in multi-particulate approaches. Owing to their potential benefits like decreased systemic toxicity, increased bioavailability, reduced local irritation, foreseeable gastric emptying time and prolonged residual time in the ascending colon, development of multi-particulate dosage forms is given importance over single unit systems. Due to their reduced particle size in relation to single unit dosage forms are competent to bypass the GIT smoothly, leading to less inter- and intra-subject variability.\textsuperscript{9,109,110}

**Conclusion**

For successful delivery of drugs to the colon, one must consider into account the gastric pH, first pass metabolism, luminal enzymatic degradation, mucin turnover and intestinal transit time which often disrupt the drug and release in the upper GIT resulting in poor colonic availability. Therefore, CTDDS is substantial for drug delivery and absorption as it offers minimizing the drawbacks outlined. However, targeting of drugs to the site specific is more likely to accomplish by employing the use of relevant polymers (pectin, chitosan, hyaluronic acid, eudragit and more) that are degraded by the existing bacterial enzymes in the colon. Various approaches such as conventional and novel approaches have been discussed in this article, having the novel approaches more precise in drug targeting. However, these approaches possess their own limitations besides their use. Therefore, pharmaceutical researchers are yet working continuously in developing more validated method to reduce its undesirable effects and increase the drug efficacy.

**Conflict of interest**

The authors do not have any conflict of interest.

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