**Scholars Academic Journal of Pharmacy**
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS

**Pharmacy**

# Colon Specific and Targeted Drug Delivery System (CDDS): A Review

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**DOI:** 10.36347/sajp.2024.v13i06.001 | **Received:** 03.04.2024 | **Accepted:** 14.05.2024 | **Published:** 04.06.2024

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**Abstract** **Review Article**

In the recent year colonic drug delivery is important for delivery of drug for the treatment of local disease. Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. This article gives overview on different approaches of colon targeted drug delivery system such as pH sensitive polymer coated drug delivery to colon, time Controlled release drug delivery to Colon microbially triggered systems, prodrug approach to drug delivery to colon it also consist of recent approaches of colon targeted drug delivery such as pressure controlled drug-Delivery Systems, Novel Colon Targeted Delivery System (CODESTM), Osmotic Controlled Drug Delivery (ORDS-CT).

**Keywords:** Colonic Drug Delivery, Targeted Drug Delivery System, Colon Microbially Triggered Systems, CDDS.



## INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs [1, 2]. The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon [3]. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability [4]. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers [5].

Oral route is the most convenient and preferred route but other routes for CDDS may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal [6]. Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity [7].

Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction

and enzymatic cleavage i.e. glycosides [8]. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration.

**Anatomy of colon**

The entire colon is about 5 feet (150 cm) long and is divided into 5 major segments. The GI tract is divided into stomach, small intestine and large intestine. Large intestine extending from the ileocecal junction to the anus and it is divided into 3 main parts. They are colon, rectum, and anal canal. Perinatal folds are called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon and hepatic flexure. The left colon consists of descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus. The colon tissue contains the villi, lymph, muscle, nerves and vessels. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which 90% of fluid is absorbed. The adult colon is line by at least 8 distinct epithelial cell types, viz columnar or absorptive cells, deep crypt secretary cells, vacuolated cells, microfold or M cells, undifferentiated crypt cells, multivesicular or caveolated cells, goblet cellsand variety of endocrine cells [13, 15, 17].

**Criteria for selection of drug for CDDS**

The best candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhoea, and colon cancer is ideal candidates for local colon delivery [9-11]. The criteria for selection of drugs for CDDS are summarized in (Table 1). Drug carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems [12].

**Table 1: Criteria for selection of drugs for CDDS**

| Criteria | Pharmacological class | Non-peptide drugs | Peptide drugs |
|---|---|---|---|
| Drugs used for local effects in colon against GIT diseases | Anti-inflammatory drugs | Oxyprenolol, Metoprolol, Nifedipine. | Amylin,Antisense oligonucleotide. |
| Drugs poorly absorbed from upper GIT | Antihypertensive, antianginal drugs. | Ibuprofen, Isosorbides, Theophylline | Cyclosporine, Desmopressin |
| Drugs for colon cancer | Antineoplastic drugs. | Pseudoephedrine | Epoetin, Glucagon |
| Drugs that degrade in stomach and small intestine | Peptides and proteins | Bromophenaramine, 5-Flourouracil, Doxorubicin | Gonadoreline, Insulin, Interferons, |
| Drugs undergo extensive first pass metabolism | Nitroglycerin, corticosteroids | Bleomycin, Nicotine | Protirelin,sermorelin, Saloatonin |
| Drugs for targeting | Antiarthritic, antiasthamatic drugs. | Prednisolone, hydrocortisone, 5-Amino-salicylic acid. | Somatropin,Urotoilitin |

**Drug absorption in the colon**

Drugs are absorbed passively by either paracellular or transcellular route. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, where paracellular absorption involves the transport of drug through the tight junction between cells and is the route most hydrophilic drug takes.The poor paracellular absorption of many drugs in the colon is due to the fact that epithelial cell junctions are very tight. The slow rate if transit in colon lets the drug stay in contact with the mucosa for a longer period than in small intestine which compensates the much lower surface area. The colonic contents become more viscous with progressive absorption of water as one travels further through the colon. This causes a reduced dissolution rate, slow diffusion of dissolved drug through the mucosa. Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum. The oral absorption of the majority of peptide and protein drugs is limited because of following reasons:

- Degradation in the acidic environment of the stomach.
- Enzymatic degradation in the small and large intestine.
- Rapid small intestine transit.
- Low mucosal permeability.
- Extensive first pass metabolism by the absorbing membrane and the liver.

**Need of colon targeted drug delivery**

It is useful for treating the disease at the site of infection and to increase the local effect of drug. Chronic colitis, namely ulcerative colitis, and Crohn's disease are currently treated with glucocorticoids, and other anti-inflammatory agents Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adeno-suppression, immunosuppression,

cushinoid symptoms, and bone resorption. Thus selective delivery of drugs to the colon could not only lower the required dose but also reduce the systemic side effects caused by high doses.

**Table 2: Colon targeted disease, drugs and types**

| Target sites | Disease condition | Drug and active agents |
|---|---|---|
| Topical action | Inflammatory Bowel Disease<br>Irratable bowel disease<br>Chrohns disease | Hydrocortisone, budenoside, prednisolone, Sulfaselazine, balsalazide |
| Local action | Pancreatactomy and cystic fibrosis , colorectal cancer | Digestive enzyme supplements<br>5 - flourosil |
| Systemic action | To prevent gastric irritation<br>To prevent first pass metabolism of orally ingested drug,Oral delivery of peptides, oral delivery of vaccines | NSAID<br>Steroids<br>Insulin<br>Typhoid |

**Advantages**

- The site specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease, irritable bowel syndrome, colon cancer.
- Used in treatment of nicotinic addiction.
- Useful for the delivery of proteins, peptides which are being delivered by injections.
- Delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most and also minimize the potential side effects and drug instability.
- Used in direct treatment of disease at that site, low dosing and less systemic side effects.
- Molecules that are poorly absorbed in the upper gut, such as peptides, proteins may be better absorbed from the lower GIT.
- The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease.
- The colon is having high water absorption capacity, the colonic contents are considerably viscous and thus availability of most drugs to the absorptive membrane is low.
- The metabolic processes like azoreduction and enzymatic cleavage are takes place in colon which is responsible for the metabolism of many drugs and peptides like insulin [17-19].

**Disadvantages**

- A longer residence time of 3-5 days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme.
- Single unit colon targeted drug delivery system has the disadvantage of un intentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology.
- Development of colon specific drug is difficult due to many biological barriers.
- Cytochrome (P450) class of drug metabolizing enzymes has lower affinity in the colonic mucosa [18, 20].

**Limitations**

- Colon offers a near neutral pH, at the site of drug delivery, reduced enzyme activity, a long transit time and increased responsiveness to absorption enhancers.
- Wide range of pH values and different enzymes present throughout the gastro intestinal tract, through which dosage form has to travel before reaching target site.
- For better drug delivery it should be in solution form before it arrives in the colon.
- Fluid content in the colon is much lower and it is more viscous than in the upper part of GI tract.
- Stability of drug is also a concern and must be taken into consideration while designing the delivery system.
- The drug may potentially bind in a non-specific way to dietary residues, intestinal secretions, mucus or fecal matter.
- The resident microflora could also affect colonic performance via metabolic degradation of the drug.
- Lower surface area and relative tightness also affects the bioavailability of drugs. (17,18)

**Newly developed approaches for colon targeting**

There are certain recent approaches for colon-targeting drug delivery systems. These techniques exploit physiological factors like luminal pressure and osmotic pressure [22].

**Pressure-controlled delivery system**

Colon content is more viscous than small intestine due to higher water reabsorption in the colon. The peristaltic movement of the colon is much more than that in the small intestine that results in increased motion in the luminal pressure at the colon. A study was performed by [25] on the development of ethyl cellulose (EC) polymers-based pressure-controlled delivery system capsules. The disintegration of the capsule was dependent on the thickness of the ethyl cellulose (EC) capsule, size and density and the drug release occur on disintegration and turned into liquid, but the colonic content is highly viscous than small intestine, so may be an obstacle for site-specific action [26]. The action of such formulation depends on the peristaltic movement of the stomach. This movement causes the breakdown of larger molecules to smaller ones and further transferred to the small intestine. And the peristaltic motion present in the small intestine moves these particles in a bolus action from one part of the GIT to another. Mass peristaltic movement in the colon which transfers the molecules or particles in the ascending colon to the transverse colon. Such movements occur only in specified amounts or times, sometimes three times a day, or four times a day. The result of these movements is an increase in the luminal pressure. Studies have taken advantage of such an increase in the luminal pressure in the development of pressure-controlled colon-targeted drug delivery [27]. For example, studies done by Amidon, S., J. E. Brown, and V. S. Dave [22] used the pressure of the colon to produce a specific drug formulation targeted at the colon, which consisted of gelatin capsules withholding the drug inside coated with ethyl-cellulose polymers which is water insoluble in the inner part of the capsule. It traps the drug within and has a suppository base that made to dissolve at body temperature after administration. The thickness of the insoluble polymer, which is ethyl cellulose (EC) decides how much the capsule disintegrated. Rangari Nalanda, T. and K. Puranik Prashant [28] saw the mechanism of this formulation. The drug enters the small intestine where water of the fluid present in the small intestine is absorbed by the capsule, increasing the viscosity and in turn, increasing pressure in the capsule, which results in drug expulsion into the colon via colonic bacteria, which degrades the swollen coating.

**Osmotic controlled delivery**

The osmotic-controlled release oral delivery (ORO-CT) system can formulate either as a single osmotic unit or may incorporated with 5-6 push-pull units and each unit is about 4 mm in diameter encapsulated in a single gelatin capsule. Each push-pull unit has an osmotic push layer and a drug layer. These layers are surrounded by a semipermeable membrane. Once the formulation is administered or swallowed, the gelatin capsules dissolve and they dissolve in small intestinal pH, dissolution media or when water enters in the system. But there is a drug impermeable enteric coating that restricts the entry of water in acidic media of the stomach. However, once the system reaches a higher or alkaline pH of the small intestine, the capsule dissolves at once and dissolution media or water penetrates the formulation. On the entry of dissolution media or water into system (formulation) causes swelling and pushes the compartment, resulting in generation of force that expels the drug out from an orifice through the membrane near the drug layer in a rate that depends on the rate of water entry into the semipermeable membrane [21, 24]. Fig 1 shows mechanism of ORO-CT. In the treatment of (UC), the compartments are designed in intervals of three to four hours post gastric delay for the prevention of drug delivery into the small intestine, in which the delay lasts until the drug has been delivered into the colon, where it is released in a constant rate of 24 h or over a short period of 4 h [29]. A new developed phase transited system showed to be a good option in the use of formulations targeted at the colon. Philip and joint author show the performance of a drug that does not disintegrate and has controlled release with a capsular system of asymmetrical membranes for flurbiprofen in which different formulation variables put under the test for their utility as a controlled release drug formulation. The results showed that the drug release was dependent on the osmotic pressure of the dissolution medium rather than pH [30].

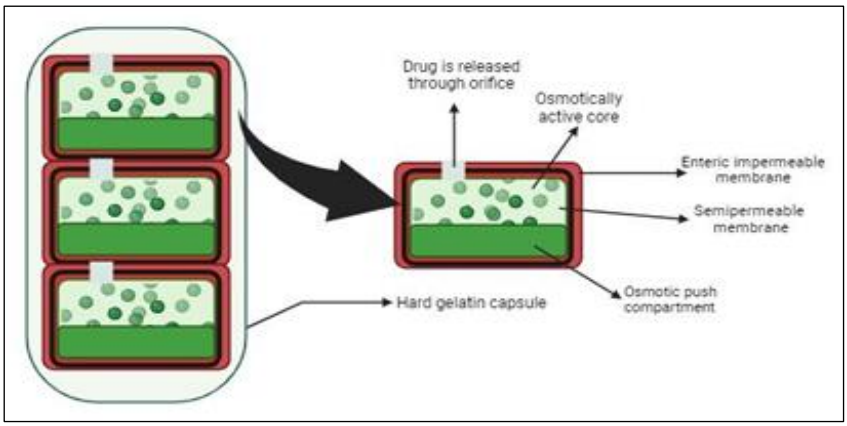


**Fig 1: Mechanism of ORO-CT drug delivery [31]**

**Newly developed CTDDS**

**CODES™**

It is a budesonide pellet based on CODES ™ technology which is pH dependent and as well as a microbial-dependent combination system [33, 34]. This combination can overcome the problems that cause limitations of pH sensitive formulations and time-dependent systems [23]. It consists of a lactulose-based core, acting as a trigger for site specific drug release in the colon. The core material coated using two different coating materials. The first coating is composed of an acid soluble material like Eudragit E and the second coating over the first coating consists of an enteric-coated material such as Eudragit L. [36]. The unique structure of CODES™ allows the drug to stay unaffected in the stomach due to the enteric coating; however, it dissolves rapidly after gastric emptying. The drug stays protected due to the presence of an acid-soluble coating. Coating dissolves in the small intestine. The pH of the small intestine is acidic, and the acidic coating of the formulation protects the release of the drug as it passes through the acidic pH of the small intestine. There is a small penetration of dissolution media and swelling of formulation in the small intestine. However, the polysaccharide (lactulose) is released in the colon and diffuses through the coverings due to the enzymatic degradation of the lactulose. It is degraded by the bacteria present in the colon, which converts lactulose to organic acid as represented in Fig 2. Such degradation alters the pH (lowering it) of the colon sufficiently for the acid soluble coating to dissolve and the drug released [23, 36, 28, 32].

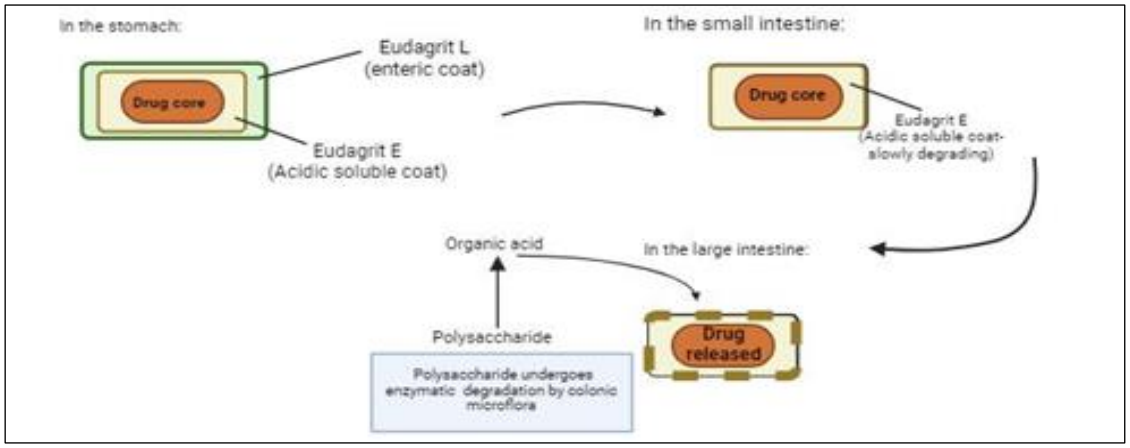


**Fig 2: Mechanism of CODES drug delivery [33]**

## CONCLUSION

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. For colon targeted drug delivery four primary approaches were proposed for CDDS: prodrugs, pH and time dependent systems and micobletriggered drug delivery system. Of these first three approaches is not ideal for CDDS. Novel approaches developed for CDDS are more specific. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. For in vitro evaluation of a colon-specific drug delivery system, it seems that more than one testing method is necessary to characterize drug release and justify system design rationale. Considering the sophistication of colonspecific drug delivery systems and the uncertainty of current dissolution methods in establishing possible in vitro/in vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon and yet can be used routinely in an industry setting for the evaluation of CDDS.

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