A Review On: Colon Targeted Drug Delivery System

Ayushi M. Pawar *1, Swapnil R. Patil2, Tushar D. Fegade1
1.Department of Pharmacology, Arunamai college of Pharmacy, Mamrabad, KBC, North Maharashtra University, Jalgaon (MH) INDIA 425001.
2.Department of Pharmaceutics, Vidya Bharati College of Pharmacy, Amravati University, Amravati, (MH) INDIA 444602.

ABSTRACT

Colon-specific drug delivery systems (CDDS) are desirable for the treatment of a range of local diseases such as ulcerative colitis, Crohn’s disease, irritable bowel syndrome, chronic pancreatitis, and colonic cancer. In addition, the colon can be a potential site for the systemic absorption of several drugs to treat non-colonic conditions. Drugs such as proteins and peptides that are known to degrade in the extreme gastric pH, if delivered to the colon intact, can be systemically absorbed by colonic mucosa. In order to achieve effective therapeutic outcomes, it is imperative that the designed delivery system specifically targets the drugs into the colon. Several formulation approaches have been explored in the development colon-targeted drug delivery systems. Colon targeting holds a great potential and still need more innovative work. This review article discusses introduction of colon, need and approaches of colonic drug delivery, factor effecting colonic transition, colonic diseases and the novel and emerging technologies for colon targeting.

Keywords: Colon targeted drug delivery, Factors affecting colon delivery; Novel approaches; Disease of colon-specific drug delivery systems.

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INTRODUCTION¹⁻⁴

Targeted drug delivery to the colon is more desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn’s disease, amebiosis, colonic cancer, and systemic delivery of protein and peptide drug. The delivery of drugs to the colon via gastrointestinal (GI) tract requires the protection of a drug from being released in stomach and small intestine. It can be achieved by the use of drug delivery system (DDS) that can protect the drug during its passage to colon. And the drug must be released in the colon from the drug delivery system. Targeting depends on exploiting a unique feature of specific site and protecting the drug until it reaches to the site. Delivery of drugs via colon offers many therapeutic advantages. Drugs, which are destroyed by the stomach acid and metabolized by pancreatic enzymes, are protected. Sustained release of drugs into colon can be useful in the treatment of certain diseases. The colonic delivery is also useful for the systemic absorption of drugs like nifedipine, isosorbide, and theophylline.

The colon is the most suitable site for absorption of peptides and protein drugs for the following reasons:

- Less degradation by digestive enzymes,
- Proteolytic activity of colon mucosa is less than that observed in small intestine, thus CDD. Protect peptide and protein drugs from hydrolysis, and enzymatic degradation in the duodenum and jejunum, and releases the drug into the ileum or colon which produces greater systemic bioavailability.

The colon has a long residence time which is up to 5 days and hence it is highly responsible for enhancement of absorption. The human colon has about 400 different species of bacteria as resident flora, the reactions carried out by this gut flora are azoreduction and enzymatic cleavage i.e. glycosides. Colon drug delivery has also gained increased importance not just for the systemic delivery of drugs for the treatment of local diseases, but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the drug reaches in to the colon.

| Target sites | Disease conditions | Drug and active agents |
|--------------|--------------------|------------------------|

Table 1: Colon targeting diseases, drugs and sites
Advantages[5-7]

- 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.

Disadvantages[8-9]

- Low dose loading.
- Higher need of excipients.
- Lack of manufacturing Reproducibility and efficacy.
- Multiple formulation steps.
- Large number of process variables.
- Need of advanced technology.
- Skilled personal needed for Manufacturing of colonic drug delivery system.

Limitations of Colonic Drug Delivery[10]
The development of a colon-specific drug delivery system is associated with specific limitations and challenges. A predominant and an obvious challenge is the fact that the colon is located in the distal part of the gastrointestinal tract (GIT). An orally administered dosage form has to traverse the entire alimentary canal in order or each the target site. The GIT physiology is complex and has a wide range of pH values, fluid volumes, and transit times. Moreover, the presence of food and metabolic enzymes also increases the physiological complexity.

These factors are an obstacle to the reliable and efficient delivery of drugs to the colon. Another factor is the drug solubility. Due to allow colonic luminal fluid volume, higher viscosity, and a neutral pH, the solubilization of the drug could be a rate-limiting factor for colonic absorption. Finally, maintaining the stability of the drug in the colon can be a matter of concern. The nonspecific interactions of the drug with the colonic content e.g., dietary residues, intestinal secretions, mucus, or fecal matter can have a negative influence on the stability of the drug. In addition, the colonic bacterial enzymes may also degrade the drug, rendering it ineffective.

Criteria For Selection Of Drug For CDDS \[11\]
CTDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are prominent for local colon delivery. Drugs used for local effects in colon against GIT diseases.
- Drugs poorly absorbed from upper GIT
- Drugs for colon cancer
- Drugs that degrade in stomach and small intestine
- Drugs that undergo extensive first pass metabolism
- Drugs poorly absorbed from upper GIT
- Drugs for targeting

Need Of Colon Targeted Drug Delivery \[12-13\]
Targeted drug delivery into the colon helpful in treatment of diseases at that site, fewer systemic side effects and dose can be minimized. Colon specific formulation is beneficial for the administration of proteins, peptide drugs and also to prolong the drug delivery. Colon targeted drug delivery is suitable for delivery of drugs which are polar and/or susceptible to the chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism. Serious diseases of the colon are treated more effectively if drugs were targeted to the colon.

Example. Colonic cancers like colorectal cancer.

Anatomy And Physiology Of GIT \[14-15\]
The GIT, also called the alimentary canal, is a muscular digestive tube that winds through the body. The GIT is a selective barrier between the environment and the systemic circulation, which functions to digest dietary food, to absorb nutrients, electrolytes and fluid, and to prevent the absorption of potentially harmful substances. The small intestine is the longest part of the GIT where most of the enzymatic digestion and virtually all absorption occur.

![Gastrointestinal Tract](image)

**Figure 1: Gastrointestinal Tract**

The large intestine is the last major subdivisions of the GIT. The digested materials that reach the large intestine contain few nutrients, but the residues remain here for 12-24 hr. Major regions of the large intestine are the cecum, colon, rectum and anal canal.

**Structure of Colon**\(^{[15, 16-18]}\)

The colon forms the lower part of the GIT and extends from the ileo-caecal junction to the anus the entire colon is about 5 feet (150cm) long which is divided into following groups.
Figure 2: Structure of Colon

**Ascending Colon**
20-25 cm long located behind the peritoneum hepatic flexure- lies under right lobe of liver.

**Cecum**
(Proximal Right Colon) 6x9cm pouch covered with peritoneum appendix a vermiform (wormlike) diverticulum’s located in the lower cecum.

**Transverse Colon**
Lies anterior in abdomen, attached to gastro colic ligament splenic flexure near tail of pancreas and spleen

**Descending Colon**
10-15cm long located behind the peritoneum. After it enters the true pelvis, it is known as a sigmoid colon.

**Sigmoid Colon**
This part describes an S-shaped curve in the pelvis that continues downwards to become the rectum.

**Rectum**
This is slightly dilated section of the colon about 13cm long. It leads from the sigmoid colon and terminates in the anal canal.

**The Canal**
Canal this is the short passage about 3.8cm long and leads from the rectum to the exterior. Both the ascending and descending colon are retroperitoneal; the transverse and sigmoid colon are not true to
its name, the ascending colon side of the abdomen, reaches the inferior surface of the liver and turns abruptly to the left to form the right colic (colic) flexure. The colon continues across the abdomen to the left side as the transverse colon. It curves beneath the inferior end of the spleen on the left side as the colic (splenic) flexure and passes inferiorly to the level of the iliac crest as the descending colon. The sigmoid colon (sigma= s-shaped) begins near the left iliac crest, projects medially to the midline and terminates as the rectum at about the level of the third sacral vertebra.

The rectum the last 20cm of the GIT, lies anterior to the sacrum and coccyx the terminal 2-3cm of the rectum is called the anal canal. The major function of the colon is the consolidation of the intestinal contents into faeces by the absorption of water and electrolytes and to store the faeces until excretion. The absorptive capacity is very high; each day about 2000 ml of fluid enters the colon through the ileo-caecal valve from which more than 90 % of the fluid is absorbed.

**pH in the Colon** [19]

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery.

**Table 2: pH of various parts in gastrointestinal tract**

| Sr.No. | Location                  | pH          |
|--------|---------------------------|-------------|
| 1      | Stomach Fasted condition Fed condition | 1.5 - 2.0 3.0 - 5.0 |
| 2      | Small intestine Jejunum Ileum | 5.0 - 6.5 6.0 - 7.5 6.4 |
| 3      | Large intestine Right colon Mid colon & Left colon | 6.7 – 7.3 6.4 6.0 - 7 |

There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine (Table 2). The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

**Gastro Intestine Transit** [16]

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time. The transit times of small dosage forms in GIT are given in Table 3.

**Table 3: Transit Times of Dosage Forms in GIT**

| Organ   | Transit Time (hrs.) |
|---------|---------------------|
| Stomach | < 1 (fasting) > 3 (fed) |
Small intestine  3 – 4  
Large intestine  20 – 30

Diseases affecting colonic transit have important implications for drug delivery, diarrhea increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant

**Colonic Absorption** [20-21]

The surface area of the colon is much less compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 hours). Different factors affecting colonic absorption were reported Passes through colon cites (Tran’s cellular transport). Passes between adjacent colonocytes (Para cellular transport). Tran’s cellular absorption involves the passage of drugs through cells and thus the route for most lipophilic drugs takes, whereas Para cellular absorption involves the transport of drug through the tight junctions between the cells and is the route of most hydrophilic drugs. Drugs shown to be well absorbed include glibenclamide, diclofenac, theophylline, ibuprofen, metoprolol and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide, bufomedil, atenolol.

**Factors Affecting Colonic Absorption** [22]

- Physical properties of drug such as pKa and degree of ionization.
- Colonic residence time as commanded by GIT motility.
- Degradation by bacterial enzymes and metabolite products.
- Local physiological action of drug.
- Selective and non-selective binding to mucus.
- Disease state.
- Transit through GIT.

**DIFFERENT APPROACHES FOR THE COLON TARGETING** [23-24]

**Azo bond conjugate**

Sulfasalazine is mainly used for the treatment of inflammatory bowel diseases. It is 5- Amino Salicylic Acid (5ASA) prodrug. 85% of oral dose of sulfasalazine reaches to the colon unabsorbed, where it is reduced by the anaerobic environment into 5-ASA and sulphapyridine. Various studies are conducted on sulphapyridine which lead to the formation of other prodrug like Olsalazine, Balsalazine, 4-amino benzoyl-β- alanine. Intestinal microflora produces glycosidase, one of prominent group of enzyme. Colon specific formulation of flurbiprofen had been evaluated by using azo-aromatic and pH sensitive polymer and it was concluded that azoaromatic polymer and pH
sensitive polymer eudragit S can successfully be used for colonic drug delivery. Pulsincap drug delivery of salbutamol sulphate had been investigated. An empty gelatin capsule was coated with ethyl cellulose keeping the cap portion as such. A hydrogel plug made of gelatin was suitably coated with cellulose acetate phthalate in such a way that it was fixed to the body under the cap. Eudragit microspheres containing the salbutamol sulphate were prepared by emulsion solvent evaporation method and were incorporated into this specialized capsule shell. In vitro dissolution results indicated that the onset of drug release was after 7 to 8 hr. of the experiment started. Mutual azo prodrug of 5-aminosalicyic acid with histidine was synthesized by coupling L-histidine with salicylic acid, for targeted drug delivery to the inflamed gut tissue.

**Glucuronide conjugate**
Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower gastro-intestinal tract secrete glucuronidase that glucouronidate a variety of drugs in the intestine. Since the glucuronidation process results in the release of active drug and enables its reabsorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery.

**Cyclodextrin conjugates**
The hydrophilic and ionisable Cyclodextrins can serve as potent drug carriers in the immediate release and delayed release-formulations, while hydrophobic Cyclodextrins can retard the release rate of water. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. Conjugates of a drug with Cyclodextrins can be a versatile means of constructing a new class of colon targeting prodrugs soluble drugs. Ibuprofen prodrugs of α-, β- and γ-Cyclodextrins were investigated. Methotrexate prodrugs of α- and γ-Cyclodextrins were also synthesized and result established the primary aim of masking the ulcer genic potential of free drug, by using 12-fold dose of the normal dose of methotrexate and equivalent doses of the esters.

**Dextran conjugates**
Dextran ester prodrug of metronidazole have been prepared and characterized. Dextran ester prodrugs of dexamethasone and methyl prednisolone was synthesized and proved the efficacy of the prodrugs for delivering drugs to the colon. Methyl prednisolone and dexamethasone was covalently attached to the dextran by the use of a succinate linker.

**Amino-acid conjugates**
Due to the hydrophilic nature of polar groups like NH2 and COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these...
polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylic acid.

**Hydrogels** [26]

Hydrogels can be used for site specific delivery of peptide and protein drugs through colon. The Hydrogels are composing of acidic commoners and enzymatically degradable azo aromatic crosslinks. In the acidic pH, gels shows less swelling that protect the drug against degradation in stomach. As the pH of environment increases i.e. become basic, swelling increases. This result is easy access of enzymes like azoreductase, which ultimately release of drug.

**Coating with pH dependent polymers** [27]

The pH in the terminal ileum and colon in higher than in any other region of the gastrointestinal tract and thus dosage forms which disintegrate at high pH ranges can be target into the region. A level of pH is higher in the terminal ileum region then in the cecum. Dosage forms are often delayed at the ileocecal junction, careful selection of enteric coat composition and thickness is needed to ensure that disintegration does not occur until the dosage from moves through the ileocecal junction from the terminal ileum into the cecum. Synonyms for eudragit are Eastacryl, Koll coat MAE, polymeric methacrylates. Delayed release tablets containing meclizine and coated with eudragit S-100 were studied. These tablets dissolved at a pH level of 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon. The formulation was successful in achieving site specific delivery of mesalazine, failure of the coating to dissolve has been reported. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose. For colonic drug delivery, drug core is coated with pH sensitive polymers. The drug are includes tablets, capsules, pellets, granules, micro-particles and nanoparticles. pH- dependent micro beads of theophylline hydrochloride were developed and evaluated by using alginate and chitosan by inotropic gelation method followed by enteric coating with eudragit S100. Investigation centered with the formulation of prednisolone containing 1% eudragit RS PM had been carried out which shows 100% drug release. Tablet containing mesalazine were investigated which was coated with two polymers eudragit L100 and eudragit S100 in combination 1:0, 4:1, 3:2, 1:1, 1:5, and 0:1. Chitosan microspheres contain Ondansetron were prepared by emulsion cross linking method. Work combines eudragit S100 and chitosan polymers. Analysis regression values suggest that the possible drug release was Pappas model.

**Table 3: Threshold pH of different polymers suitable for pH dependent drug delivery** [28]
Timed released systems[^29]

It is based on the concept of preventing the release of drug 3–5 hr. after entering into small intestine. (Example: Pulsatile release, Pulsincap, Delayed release, Sigmoidal release system) In this approach, drug release from the system after a predetermined lag time according to transit time from mouth to colon. The lag time depends upon the gastric motility and size of the dosage form. One of the earliest approaches is the Pulsincap device. This device consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug, which is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine, the enteric coating dissolves and the hydrogel plug starts to swell. The amount of hydrogel is adjusted so that it pops out only after the stipulated period of time to release the contents. In another approach, organic acids were filled into the body of a hard gelatin capsule as a pH adjusting agent together with the drug substance. The joint of the capsule was sealed using an ethanolic solution of ethyl cellulose. The capsule was first coated with an acid soluble cationic polymer, then with a hydrophilic polymer hydroxypropyl methylcellulose and finally enteric ally coated with hydroxyl propyl methyl cellulose acetate succinate. After ingestion of the capsule, the outermost enteric layer of the coating prevents drug release in the stomach.

The enteric layer and the hydrophilic layers dissolve quickly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid, the acid soluble layer dissolves and the enclosed drug is quickly released. Pressure controlled drug delivery systems: This approach relies on the strong peristaltic waves in the colon that lead to a temporarily increased luminal pressure. In the upper GIT, the drug delivery system is not directly subjected to the luminal pressure, since sufficient fluid is present in the stomach and small intestine. Due to raised luminal pressure in the colon, the system raptures and releases the drug. Colon modulated drug delivery system of salbutamol sulphate had been developed for the treatment of nocturnal asthma. The cores containing salbutamol sulphate were prepared by direct

[^29]: Patil et al., Am. J. PharmTech Res. 2020; 10(02) ISSN: 2249-3387
compression method use of microcrystalline cellulose and effervescent agent (sodium bicarbonate) and then coated sequentially with an inner swelling layer containing a hydrocolloid (hydroxyl propyl methylcellulose E5) and an outer rupturable layer having eudragit RL/RS (1:1). Drug delivery system was investigated which was built on the principles of the combination of pH and time sensitivity. Press-coated melamine tablets with a coat of HPMC E-15 were over coated with eudragit S100. A novel time and pH dependent system was investigated. The system consists of the core tablet of mesalamine which is compression coated with hydroxypropyl methylcellulose (HPMC K4M). This is then coated with eudragit L100. The result revealed that as the amount of HPMC increases, the lag time and t50 value also increases. Osmotic pressure controlled systems: The unit reaches intact to the colon where drug release takes place due to osmotic pressure generated by the entry of the solvent. It is also known as OROS.

**Redox sensitive polymer coating** [30]

Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzes non enzymatically by enzymatically generated flavins are being developed for colon targeting. A common colonic bacterium, Bacteroides fragilis was used as test organism and the reduction of azo dyes amaranth, Orange II, tartrazine and a model azo compound, 4, 4'- di hydroxy azobenzene were studied. It was found that the azo compounds were reduced at different rates and the rate of reduction could be correlated with the redox potential of the azo compounds. Bio adhesive systems: Bio adhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide polypropyline oxide copolymers have been investigated as materials for bio adhesive systems.

**FACTORS AFFECTING COLON DRUG DELIVERY**

They are many factors affecting colon drug delivery which are categorized into two: physiological and pharmaceutical factors.

**Physiological factors**

**Transit time in intestine and colon** [31-34]

According to the research conducted by Mayo Clinic researchers in 21 healthy people, it showed that the transit time averaged 53 hours in total. While comparing with other parts of GI tract, passage of any material through colon is very slow and takes about 40 hours. Show that the transit time of UC or IBD patients change evidently. For entering the colon in appropriate form, the drug delivery
system must go beyond all the barriers in stomach and small intestine. The dosage form takes about 3-4 hours to reach ileocecal junction. Presence of certain enzymes in small intestine can impose changes in the dosage form. The release of medicament from dosage form is controlled by factors like microbial flora in the colon, habitation enhancement with longer passage time.

**Gastric emptying** [35-37]

Gastric emptying and passage of bowel plays an important role in governing drug delivery to the colon by oral administration. The matter of issue when the dosage form reaches the stomach is the duration in which it will remain in the stomach before reaching the duodenum. The gastric emptying process varies according to the phases of stomach when the drug is administered. Once the drug reaches the colon, particle size plays a key role in judging the transit time of dosage form. Usually smaller particles can easily pass through the colon than larger ones. It usually completes in 5-10 minutes up to 2 hours. A colonic drug delivery system is efficient if it remains only for some time in stomach. Thus, an efficient delivery system can release drug at a far place from the colon. A person affected with diarrhea has little transit time while a person affected with constipation have larger transit time.

**Stomach and intestinal pH** [38-40]

The presence of enteric coatings on the drugs makes the pH of the GIT an important factor. In a healthy adult the pH in stomach ranges from 1.5 to 3.5 which are highly acidic and in duodenum the pH increases to 6. Gradually pH reaches 7.4 in the small intestine and then drops to a pH range 5.5-7 in the colon but this can differ depending on the individual variations, presence of food, condition of person whether healthy or diseased etc. Colon drug delivery is formulated mainly based on the pH and this pH gradient triggers the drug release. A drug is usually enclosed by a polymer coating to aim the drug at specified location, to protect the acid labile drugs from gastric fluid and to prevent GI disturbances due to irritation from the drug. Some polymers used for enteric coating are hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate and acrylate polymers which disintegrate only in the intestinal pH thus enhancing drug bioavailability specifically at colon.

**Colonic micro flora and enzyme** [41-43]

The GIT is often referred to as the store house of a large number of microorganisms that are capable of producing several enzymes which can accelerate metabolism process. This micro flora of the colon holds a variety of applications in health and for treating GI disorders like IBD. Peristaltic movement and the contents in GIT control the growth of this micro flora. The increased concentration of micro flora becomes prominent in the terminal ileum and lead to high levels in the
colon. The microbial bacteria have the potential to catalyze an enormous number of metabolic activities in the body. The enzymes produced by microbial flora mainly glycosidase and azoreductase possess the ability to release the drug in the colon. Sulphasalazine, a sulphonamide used for intestinal infection, is a prodrug that is converted to m-amino salicylic acid (having an anti-inflammatory effect on colon; prevents systemic absorption and hence increases the duration of action) and sulphapyridine (antibacterial effect) by azoreductase. Gut micro flora actively hydrolyzes a large number of polysaccharides which leads to the opportunity of making drug carriers out of naturally occurring bio polymers.

**Gastrointestinal disease condition** [44-46]

The existence of different gastrointestinal diseases like IBD, constipation, diarrhea alters the drug delivery system in colon. IBD can reduce the surface area and decrease the diffusion rate of drugs due to the thickening of mucosa and sub mucosa thus leading to malabsorption of lipophilic drugs. While diarrhea reduces the retention time and hence decreases the drug absorption and release from dosage form.

**Pharmaceutical factors** [47-48]

**Drug candidates**

An increase in absorption of weakly absorbed agents like peptides occurs because colon offers a high time for these agents to stay in it. Drug molecules used to cure GIT disorders can also be used for colon targeted drug delivery.

**Drug carriers**

The factors like drug nature, its indication are used a tool for selection of CDDS carriers. Apart from this, other factors involved are functional group of drug molecule, chemical nature, its stability factor, constant factors like partition coefficient etc.

**DISEASES RELATED TO COLON** [49-53]

**Inflammatory bowel diseases**

The two inflammatory bowel diseases (IBD) that lead to chronic inflammation and associated extra intestinal manifestations in the gastrointestinal (GI) tract are Crohn’s disease and ulcerative colitis.

The major symptoms associated with IBD are abdominal cramps and pain, diarrhea, weight loss and bleeding from intestine. More than 600 000 Americans have some kind of IBD every year.

**Crohn’s disease**

Crohn’s disease is a disease characterized by inflammation or swelling in any part of GIT mostly rectum. The inflammation can become so intense that it can penetrate the lining of the affected part. The result of the disease could be pain and diarrhea. Scar tissues are produced when the inflammation
is chronic. The factors affecting this disease are genetic, immunologic, infective agents. Cyclosporine is the drug which is used orally to treat the disease.

**Ulcerative colitis**

In this disease inner linings of large intestine, usually the lower section, colon and rectum is affected which produces inflammation and ulcers or sores. This disease usually begins in the rectal area and extends through the entire large intestine. Repeated inflammation leads to thickening of the wall of the intestine and rectum with scar tissue. The symptoms of this disease are bleeding, abdominal discomfort and diarrhea.

**Colorectal cancer**

Colorectal cancer is the cancer that starts either in the colon or the rectum. Appearance of blood in stool, diarrhea, constipation, abdominal pain, cramps, blotting, weight loss, and feeling of fatigue are the symptoms of the disease. The smart drug delivery system has proved clinical benefits in the treatment of above mentioned colon diseases.

**INTEGRATED APPROACHES FOR ACHIEVING COLONIC DELIVERY** [54-58]

In recent years, several integrated approaches have been explored to achieve colon-specific drug delivery. These approaches utilize physiological factors such as luminal pressure, or physical phenomena such as osmotic pressure in the design of the delivery systems.

**Pressure Controlled Delivery**

Peristaltic motion causes the luminal pressure of the large intestine to increase more than that of the small intestine because its contents are more viscous due to the reabsorption of water several studies have been carried out to utilize the colonic luminal pressure to develop colon-specific drug delivery systems. Takaya et al. developed capsules that deliver a drug to the colon based on luminal pressure. Although these systems allow for drugs to be delivered to the colon rather than the small intestine due to higher colonic pressure, reabsorption of water from the colon causes its content to be highly viscous which may become an obstacle for site-specific delivery.
Osmotic Controlled Delivery

Although the concept of osmotic controlled drug delivery has been around for several years, the applications of this technology in the design of colon-specific oral dosage forms have gained popularity only in the 10–15 years. The OROS-CT is an example of a system regulated by osmotic pressure. It consists of a hard gelatin capsule which dissolves in the pH of the small intestine and allows water to enter the unit. This then cause sitto swell and the drug is forced out within each capsule there can be as many as 5 –6 units, and each unit is surrounded by a drug impermeable enteric coating which prevents water from entering in the acidic environment of the stomach (Fig. 3). However, this coating dissolves and the water enters once the capsule enters the higher pH of the small intestine. Within the enteric coating there is a semipermeable membrane which encompasses an osmotic push compartment as well as a drug compartment. The water causes the push compartment to swell and form sagelin the drug compartment that is forced out of an orifice through the membrane next to the drug compartment. The rate at which the drug flows out depends on the rate at which water enters. To prevent drug release in the small intestine, these systems can also be designed such that there is a lag time between when the enteric coating dissolves and the drug is released

Pulsincap Systems
Time-dependent systems are not always side al for delivering drugs to the colon due to variability in the gastric emptying time and the changes in gastrointestinal transit due to peristalsis or disorders such as IBS. Therefore, the integration of a timed

![Mechanism of the pulsincap colon-targeted drug delivery system](image)

**Figure 4: Mechanism of the pulsincap colon-targeted drug delivery system**

Release system with pH-sensitive properties can be beneficial in achieving colon-targeted delivery. A pulsincap system is one example of a formulation that utilizes both these techniques. The system consists of a water insoluble capsule body containing the drug, a hydrogel plug which seals the opened end of this capsule body and a water soluble cap which covers the hydrogel plug (Fig.4). Additionally, the capsule is coated with an acid insoluble film coating which prevents the drug from being released in the stomach. The hydrogel plug begins swelling when this enteric coating dissolves in the small intestine. The swelling of the plug allows for a lag time before the drug is released and the amount of lag time depends on the length of the plug and the extent at which it is inserted.

Abraham et al. developed a pulsincap system in which they tested several polymers as the plug material. The formulations were tested at pH 1.2 for 2 h to simulate gastric fluid, pH 7.4 for 3 h to simulate intestinal fluid, and pH 6.8 for 7 hr to simulate the colon.

The study found that no significant drug release occurred within 5 h from the start of the experiment, and it was concluded that this modified pulsincap system can successfully target metronidazole to the colon.

**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. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Better colonic delivery could be achieved by protecting the drug from absorption and/or the environment of the upper GIT and then abruptly released in to proximal colon, which is the site for colonic targeted delivery of drugs. All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbed drugs. The colon is rich in microflora which can be used to target the drug release in the colon. To ensure a balance between efficiency, target-specificity, cost, and patient compliance, it appears that a combination of conventional and newer approaches is the key to the development of colon-specific drug delivery system.

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