INTRODUCTION
Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs (degraded by digestive enzymes of stomach and small intestine) but also for the delivery of low molecular weight compounds used to treat diseases associated with the colon or large intestine such as ulcerative colitis, diarrhea, and colon cancer. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en 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. 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\textsuperscript{2}. 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\textsuperscript{3}. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers. The colon specific drug delivery system (CDDS) should be capable of releasing the drug in 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 reaches the colon. Because the colon has a long residence time 72 hours and high water content it favors absorption of poorly absorbed drug molecule may have an improved bioavailability, CDDS has been employ to achieve following objectives i) Sustained delivery to reduce dosing frequency ii) Delay deliver of drug to achieve high Concentration in treatment of disease of distal gut iii) to delay than in upper GIT, which is the limiting factor for poorly soluble drugs.

**ANATOMY AND PHYSIOLOGY OF COLON**

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus. The human colons were shown in Figure No.1. The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed\textsuperscript{4}.

**NEED OF COLON TARGETED DRUG DELIVERY**\textsuperscript{4}

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn’s disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.
Factors Affecting Colon Targeted Drug Delivery

1. Physiological factors
2. Pharmaceutical factors

1. Physiological factors
   a. Gastric emptying
   Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times.

   b. pH of colon
   The pH of GIT varies between different individuals. The food intakes, diseased state, etc. influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site.

   c. Colonic micro flora and enzymes
   The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. Growth of this micro flora is controlled by the GIT contents and peristaltic movements. The enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT.

2. Pharmaceutical factors
   a. Drug candidates
   Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.

   b. Drug carriers
   The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. The various physicochemical factors of drug that effect the carrier selection includes chemical nature, stability, partition coefficient, functional groups of drug molecule etc.

Polymers Used in Colon Targeting

Polymer contains a large number of structural unit joined by same type linkage, form into a chain like structure. These are nowadays used in formulating various pharmaceutical products. Naturally found polymer, which include gummy exudates, proteins, enzymes, muscle fibre, polysaccharides. In olden days natural polymers are widely used in pharmacy but a variety of synthetic polymer are used nowadays for pharmaceutical and cosmetic development, using these. Polymer many therapeutic system of body namely controlled drug delivery systems, are achieved.

Natural polymer
Guar gum, Pectin, Cyclodextrin, Dextran, Amylase, Chitosan, Chondrotin sulphate, Locust bean gum.

Synthetic polymer
Shellac, Ethyl cellulose, Cellulose acetate phthalate, Hydroxy propyl methyl cellulose, Eudragit, Poly vinyl acetate phthalate.

APPROACHES USED FOR SITE SPECIFIC DRUG DELIVERY TO COLON

Several approaches are used for site-specific drug delivery. Among the primary approaches for CDDS, These include:

Primary approaches of colon specific drug delivery system

A. PH- dependent delivery
In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve in the lower small
intestine and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileocecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.

Most commonly used pH dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit S, more specifically Eudragit L and S. Colon targeted drug delivery systems based on methacrylic resins has described for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxen. Dissolution studies performed on the mesalazine tablets further confirmed that the release profiles of the drug could be manipulated by changing the Eudragit L100-55 and Eudragit S100 ratios within the pH range of 5.5 to 7.0 in which the individual polymers are soluble respectively, and a coating formulation consisting of a combination of the two copolymers can overcome the issue of high GI pH variability among individuals.

Delayed (Time controlled release system) release drug delivery to colon

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising. However due to potentially large variation of gastric emptying time of dosage forms in humans, in this approach colon arrival time of dosage forms can not accurately predicted, resulting in poor colonical availability. The dosage forms may also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5 hours (range 5 to 6 hours). Disadvantages of this system are- (i) Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake. (ii) Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug. (iii) Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea and the ulcerative colitis.

Microbially triggered system

These systems are based on the exploitation of the specific enzymatic activity of the microflora (enterobacteria) present in the colon. The colonic bacteria are predominately anaerobic in nature and secrete enzymes that are capable of metabolizing substrates such as carbohydrates and proteins that escape the digestion in the upper GI tract. Bacterial count in colon is much higher around 1011-1012 CFU/ml with some 400 different species which are:

Fundamentally aerobic, predominant species such as Bacteroides, Bifid bacterium and Eubacterum etc., whose major metabolic process occurring in colon are hydrolysis and reduction. The enzymes present in the colon are:

1. Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.
2. Hydrolytic enzymes: Esterases, Amidases, Glycosidases, Glucuronidase, sulfatase etc.

(i) Prodrug approach for drug delivery to colon

Prodrug is the main approach of microbial triggered drug delivery system in which the drug release from the formulation is triggered by the microflora present in the gut. Prodrug is the inactive form of an active parent drug that undergoes enzymatic transformation to release the active drug (Figure No.2). The produrgs are prepared by linking the active drug with hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose, etc.

(ii) Polysaccharide based delivery systems

Polysaccharide based delivery system is the other form of microbial triggered drug delivery system. Naturally occurring polysaccharides like guar gum, xanthan gum, chitosan, alginates, etc. are used in targeting the drug delivery. These are broken down by the colonic micro flora to simple saccharides.

B. Newly developed approaches for CDDS

a) Pressure-controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine, have developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is...
insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the 10. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human11.

b) Pulsatile colon targeted drug delivery
i) Pulsincap system
In this system (Figure No.3) the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), polymethyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body12.

ii) Port system
In this system (Figure No.4) the capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation. When the capsule comes in contact with the dissolution fluid the semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals13.

c) Osmotically controlled system (ORDS- CT)
The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable14. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled through the membrane next to the drug layer (Figure No.5). Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7).

D) CODES technology (combination of pH dependent and microbially triggered CDDS)
This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine. This system consists of a core tablet coated with three layers of polymer coatings. The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes through the pyloric and duodenum and exposes the next coating. The next coating is composed of Eudragit E. This layer allows the release of lactulose present in the inner core. This released lactulose gets metabolized into short chain fatty acids that lower the surrounding pH where the Eudragit E layer dissolves. The dissolving of Eudragit E results in the exposure of the drug. The other polysaccharides that are used along with the drug in the core tablet are mannitol, maltose, etc. The bacteria present in the colon are responsible for the degradation of polysaccharides that are released from the core tablet. The degradation of polysaccharides results in
organic acids formation that lowers the pH of the contents surrounding the tablet (Figure No.6).

**Multi particulate system based drug delivery**

The various advantages of multiparticulate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The various multiparticulate approaches include pellets, micro particles, granules and nanoparticles. Multiparticulates systems are preferred over single unit dosage forms as the multiparticulate systems enables the drug to reach the colon quickly and retained in colon for long period of time. These systems pass through the GIT easily due to their smaller size. Multiparticulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption. Nanoparticles, the preparation of nanoparticles is simple and these are capable of protecting the protein and peptide drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium. The polymeric nanoparticles are prepared by various techniques like polymerization, nanoprecipitation, inverse micro emulsion. The methods involve the use of organic solvents, heat and agitation. The drawback of these methods is that the heat, agitation is harmful to proteins and peptide drugs. Ionic gelation technique is the most widely used method for proteins and peptide drugs.

**Evaluation test of Colon Drug Delivery System**

**In vitro evaluation**

No standardized evaluation technique is available for evaluation of CDDS as an ideal in-vitro model should possess in-vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and components of food. These conditions are influenced by diet and physical stress. The in-vitro evaluation of colon targeted drug delivery systems includes the in-vitro dissolution study and in-vitro enzymatic test.

**1. In-vitro dissolution test**

The dissolution testing is done using the conventional basket method. The dissolution testing is done in different buffers to characterize the behavior of formulations at different pH levels. The different media that are used for the dissolution testing of colon targeted drug delivery are pH 1.2 to simulate gastric fluid, pH 6.8 to simulate small intestine, pH 7.4 to simulate large intestine. The colon targeted drug delivery systems are tested for 2hr in 0.1N HCl, 3hr in pH 6.8 phosphate buffer and finally at pH 7.4 phosphate buffer. Buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems.

**2. In-vitro enzymatic test**

There are 2 tests for the in-vitro enzymatic test.

- The carrier drug system is incubated in fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals is determined.
- Drug release study is performed in buffer medium containing enzymes pectinase, dextranase or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is directly proportional to rate of degradation of polymer carrier.

**3. In-vivo evaluation**

The in-vivo evaluation of the CDDS is done in dogs, guinea pigs, rats and pigs as they resemble the anatomic and physiological conditions, micro flora of human GIT. The distribution of various enzymes in GIT of rat and rabbit is comparable to that in human.
Figure No.1: Anatomy of colon

Figure No.2: Prodrug approach for CDDS

Figure No.3: Drug release mechanism of Pulsincap system

Figure No.4: Drug release mechanism of ORT system

Figure No.5: Osmotically controlled CDDS

Figure No.6: CODES system
CONCLUSION
Colon targeted drug delivery system offers benefits of local and systemic effects. The main advantage of CDDS is that the colon offers near neutral pH, a long transit time, reduced enzymatic activity and increased responsiveness to absorption enhancers. The novel approaches are more specific compared to the primary approaches. The biodegradable polymers are used for the colon specific delivery of the drug. For the invitro evaluation of the system the current dissolution techniques are not suitable. Research is going on to develop suitable dissolution methods to evaluate the colon targeted drug delivery systems.

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CONFLICT OF INTEREST
We declare that we have no conflict of interest.

REFERENCES

