Colon Specific Drug Delivery System: Innovative Approaches to Treat Colonic Ailments

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ABSTRACT
The present review is based on the targeting of drug to the colon by means of various approaches. This review will project the utilities and advantages of colon-targeting as it has number of implications in the field of pharmacotherapy. The current developments make a histrionic change in colon specific drug delivery system. Drug Selection to target to colon via oral route is way challenging, nevertheless newly developed approaches safeguard the drug from dilapidation and allowing appropriate release within the abdomen and small intestine. Being a potential site for the systemic absorption of several drugs, lift its demand to treat non-colonic conditions. The researchers have breakthrough the extent of delivering systems to the height where position of disease can be detectable by Enterion capsule and swallowable camera capsules are developed so as to detect the images used to diagnose a number of diseases, hence provide necessary information for the treatment of diseases. Another approaches called CODESTM, Robotic Beetle is used for direct therapy for small intestine Polyps and Tumor. Additionally, this study will portray the factors influencing colon targeting, colonic bioavailability and limitations allied with CDDS. This will also provide certain discussion of various conventional and novel technologies currently being employed for colon targeting.

Keywords: Colon targeting, Bioavailability, Novel technologies, CODESTM

INTRODUCTION
Drug targeting to colon is an active area of research for local diseases which are affecting colonic part of GIT. This therapy empowers drug to reach to the colon by various approaches and hence rendering localized treatment which reduces the toxicity of drug and enhancing the its efficacy. This has become a great demand for the treatment of local diseases associated with the colon such as Irritable Bowel Syndrome (IBS)includes Crohn’s Diseases and Ulcerative Colitis, amoebiasis, Colon Cancer etc. and also for systemic delivery of drugs like proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents.1,2
There are different approaches for targeting drug to colon which resist the drug to release in acidic environment in upper part of GIT. The route of drug delivery to colon can be oral or rectal. The oral route has extended its journey and preferred due to flexibility in their manufacturing, designing dosage form, patient compliance, safest administration and do not require sterilized preparation, whereas rectal delivery is challenging to target on specific site within colon in terms of drug distribution at different rectal dosage form which depends on their spreading capacity and retention time. The human colon has over 400 distinct residential flora of bacterial species and a possible population of up to 1010 bacteria per gram of colonic contents which helps in degradation of gut content by azo reduction and enzymatic cleavage is responsible for metabolism of drug. The colon is fascinating interest as a site where poorly absorbed drugs can be absorbed easily due to high holding time in colon and this can be increased either by application of dense enteric coated layer of polymer or by introducing extremely slow releasing matrices. Some of the approaches for colon targeting are pH sensitive polymer coating, prodrug formation, time dependent released systems, pressure or osmotically controlled system etc. Jain et al focussed on fundamental aim of drug targeting to the cancerous cells by signifying the virtues of the fledgling medical field, “nanocarriers” including liposomes, polymer based nanoparticles, metal based nanoparticles, dendrimers, protein linked systems, co-polymers and fullerenes and so on. These systems have set a platform which have been proven remarkably proficient in enhancing drug distribution and bioavailability, therefore, increasing half-life, achieving targeted drug delivery which ultimately reduces toxicity. This study also mentioned the updates on recent clinical trials in nanocarrier based therapy for colorectal cancer.

Advantages of colon drug targeting system

There are various advantages of colon targeting of which some are as below:
1. Direct drug availability at the target site.
2. Lesser amount of dose required.
3. Reduces side effects and prevent gastric irritation in case of NSAIDS administration.
4. Improves drug utilization and patient compliance.
5. Helps in maintain steady state by reducing fluctuation and maintaining safety margins.
6. High retention time increases the bioavailability of poorly absorbed drug at the site of action.
7. Provides suitable environment for drugs sensitive to gastric and digestive enzymes such as Vaccines, Proteins, and Peptides.
8. Reduces first pass metabolism.
9. Cost effective due to less dose frequency.

Limitation of the colon targeted drug delivery system

1. Required appropriate *in-vitro* dissolution testing method.
2. Fabrication of colon targeting delivery system is intricated due to a low colonic luminal fluid volume, higher viscosity, and a neutral pH and wide range of microflora affects the colonic absorption rate.
3. The drug stability is the foremost concern as it potentially binds non-specifically to dietary residues, intestinal secretions, mucus or faecal matter.
4. Incomplete release of drug whereby decreasing the bioavailability of drug.
Anatomy of Colon
The gastrointestinal tract is about 5 meters long consists of parts from mouth to anus, which is further categorize to upper GIT and lower GIT. This review is focusing on colon which is situated in the lower GIT portion includes caecum, colon and rectum. The colon is about 1.5 cm long, covering the major part of large intestine located in the abdominal cavity or behind it in retro peritoneum. Colon consists of ascending colon, hepatic flexures, transverse colon, splenic flexure, descending colon and Sigmoid colon. Ascending colon is about 20 cm long that goes from the bend on the right side underneath the liver and the caecum. Hepatic flexure is situated on the right side near the liver forming the right angle bend to colon joining ascending and transverse colon. Transverse colon is the largest about 45 cm long and most itinerant part of the colon with maximum absorption at this site and provide attachment of ascending colon to the descending colon by crossing the abdominal cavity. Its diameter diverges from 9 cm in caecum to 2 cm in sigmoid colon with average diameter is about 6.5 cm. Descending colon is about 30 cm long situated inferiorly along the left abdominal wall to the pelvic region. Sigmoid colon is connects the rectum and about 40 cm long. It is about 40 cm long forming an angle medially from the pelvis to form an S-shaped curve. The colon is the part where maximum absorption takes place owing to its high transit time of about 20 to 35 hrs and diversity in pH, large range of enzymes and about 700 species of microflora helps in digestion and metabolism of digested food.

Factors to be considered for colon targeting drug delivery system
There are various factors which may influence the formulation/development of a colon-specific drug delivery system and the colonic bioavailability of the drugs. Some of these factors are based on intrinsic and extrinsic factor which are briefly discussed below.

1. Intrinsic Factors:
   a) Intestinal colonic transit time
   b) Fluid volume of colon
   c) pH of colon
   d) Colonic microflora and enzymatic metabolism
   e) Colonic drug absorption
   f) Colonic luminal content viscosity

2. Extrinsic factors:
   a) Drug candidate
   b) Polymeric drug carrier

1. Intrinsic Factors.
   a. Intestinal colonic transit time. The transit time of colon ranges from 30 to 50 hrs is highly mutable and also influenced by number of factors such as diet, in precise dietary fibre content, mobility, stress, colonic disease and drugs. Size of the particles is dependent on the transit time of dosage form where smaller particles have more transit time than that of larger particles. Chief influence on retention of drugs varied during diseased state by margining the colonic times by about 24 hrs than a healthy subject of approx. 52 hrs and also significantly increase the stool weight with the presence of active disease presumably due to exudates form inflamed epithelium, increased mucus secretion and reduction in reabsorption of fluid and electrolytes. The studies reported that the
dosage forms colonic times usually depends on the administration time, presence/absence of food, and the type of dosage form brings about delayed during sleep, and larger dosage forms, e.g., capsules transited faster than smaller dosage forms comparatively, e.g., dispersed particles states.\textsuperscript{18,19,20}

b. Fluid volume of colon: The human food is very rich in mainly undigested proteins, carbohydrates, and fats which may acts as substrates for the microbial enzymes in the colon. The high water absorption capacity of colon approx. 90\% resulting less colonic volume where dissolution of dosage forms become challenging thereby reduce its bioavailability. The colonic fluid volume is intended to be in the range of 1-44 ml with an average volume of approximately 13 ml.\textsuperscript{21,22,23}

c. pH of colon: Target drugs to colon is very complicated task because of wide and different pH throughout GIT such as acidic to alkaline from stomach to small intestine which again declines from end of small intestine to colon and gradually increases to colon. The pH of the GIT subject to in equalities prejudiced by Diet, diseased state and food intake by the GI fluid have been used as a means for targeted colon drug delivery. Polysaccharides undergo fermentation in carbohydrate rich diet by colonic bacteria and subsequent formation of short chain fatty acids and similarly, polysaccharide-based drugs may also alter colonic pH. The pH of the colon influence solubility of drug which affects the pharmacokinetic and pharmacodynamic behaviour of a Colon Drug Delivery System. This change in pH is the basis of development of site specific colon targeting and more pronounced on drug release by coating pH sensitive of polymers.\textsuperscript{24,25,26,27,28}

d. Colonic microflora and enzymatic metabolism: A large number of anaerobic and aerobic species of bacteria are present in the entire length of the human GIT containing several hydrolytic and reductive metabolizing enzymes which are used to activate drug release in numerous parts of the GIT. The colonic enzymes catalyse and undergo several reactions, comprising the metabolism of xenobiotics (e.g., drugs) and other biomolecules (e.g., bile acid), disabling harmful metabolites as well as carbohydrate and protein fermentation. Many studies have reported that 20 - 30\% over 400 species of bacteroid genus have been found in a concentration of around 1000 CFU / mL. The polysaccharides such as chitosan, guar gum, pectin, etc are known to be resistant to gastric and intestinal enzymes, butare metabolized by anaerobic bacteria in the colon are commonly employed as release rate-controlling components in colon-targeted dosage forms.\textsuperscript{29-35}

e. Colonic drug absorption: Absorption of drug by passive transport by either paracellular or transcellular route. Transcellular absorption takes most lipophilic drugs involves the passage of drugs through cells, where paracellular absorption takes most hydrophilic drug involves the transport of drug through the tight junction between cells.\textsuperscript{36} Due to high transit time and maximum absorption of water reduces the dissolution rate, slow diffusion of dissolved drugs through mucosa. Glucocorticoids such as dexamethasone and methyl prednisolone administered by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppression, cushinoid symptoms and bone resorption.\textsuperscript{37} Thus selective delivery of drugs to the colon could not only reduce the desired dose but also diminish the systemic side effects caused by high doses.\textsuperscript{38}

f. Colonic luminic content viscosity: Higher the absorption of water in colon, higher the viscosity of the colonic luminal contents than upper GIT contents thus lowers the
dissolution rate. Additionally, the dissolution and absorption gradually decreases as the viscosity of the contents progressively increases during transition of content from ascending to descending colon. Viscosity also impacts the penetration of the drug into the disease-causing bacteria in the colon. The mobility of bacteria in the colon has been shown to be dependent on the viscosity of colonic contents.  

2. **Extrinsic factors.**  
   a. **Drug candidate:** Selection of drugs depends on nature of the drug includes chemical nature, solubility, stability, partition coefficient, functional groups of drug molecule etc. If drugs show poor absorption from the stomach or intestine including peptide are most suitable for colon targeting. The drugs used in the treatment of IBD, ulcerative colitis, diarrhoea and colon cancer are ideal for local colon delivery.  
   b. **Polymeric drug carrier:** Polymer contains a chain like structure with large number of structural unit and is widely used in various pharmaceutical formulations. Both synthetic and naturally occurring polymers have wide range of utilization in development of novel formulations owing to its favourable physicochemical properties of swelling, inert and biodegradation as well and may use as matrices and hydro gels or coating agents. Natural polymers includes Guar gum, Inulin, Pectin, Cyclodextrin, Dextran, Amylase, Chitosan, Chondrotin sulphate, Locust bean gum whereas synthetic polymers are Shellac, Ethyl cellulose, Cellulose acetate phthalate, Hydroxy propyl methyl cellulose, Eudragit, Poly vinyl acetatephthalate.  

**Approaches for Targeted Drug Delivery**  
1. **Primary Approaches**  
   1.1. Prodrug- Drug carrier covalent linkage (azo- bond conjugation/Azo polymeric prodrug)  
   1.2. Glycoside conjugation  
   1.3. Glucuronide conjugation  
   1.4. Cyclodextrin conjugation  
   1.5. Dextran conjugation  
   1.6. Amino acid conjugation  
   1.7. Polymeric prodrug  
2. **Newly Developed Approaches**  
   2.1. pH dependent  
      2.1.1. Drug core coating with pH sensitive polymer  
         • Eudracol™  
         • Danbiosys (Targit™) technology  
      2.1.2. Embedding in pH sensitive matrices  
2.2. Delayed (Time controlled released system)  
   2.2.1. Time clock® system  
   2.2.2. For caps- pH sensitive and time release based  
   2.2.3. Time controlled explosive® system  
   2.2.4. Chronotropic® system  
   2.2.5. Pulsatile CDDS
2.3. Microbially triggered CDDS (Enzyme based)

2.3.1. Polysaccharide based

- Coating with biodegradable polymer
  - Colal-Pred™ system
  - Codes™ Technology

- Embedding in biodegradable polysaccharides

- Hydrogel

- Pressure dependent
  - Pressure controlled drug delivery system
  - Osmotic delivery (OROS-CT delivery & Osmet pump)

2.3.1.5. Multiparticulate system

- Pellets
- Beads
- Microspheres
- Nanoparticles

2.3.2. Prodrug based

1. Primary approach:

1.1. Prodrug based drug carrier covalent linkage:

Prodrugs are pharmacologically inactive derivatives of a drug molecule which requires being hydrolysing and enzymatically transforming to release the active ingredient such as those in colon.\textsuperscript{45} Optimal drug delivery specific to the colon requires minimal release in the upper portions of the gastrointestinal tract and much more extensive in the colon. Preparation of conjugates are meant to be the one of the profound solution and have been broadly researched and categorized.\textsuperscript{46} Metabolism of azo compounds by intestinal bacteria for metabolic process. A number of other covalent linkages forming conjugates to hydrophobic moieties like amino acids, glucuronic acids, glucose, galactose, cellulose etc. susceptible to bacterial hydrolysis especially in the colon.\textsuperscript{47} Kim et al. have studied metabolism of prodrug of metronidazole to active drug in rats cecal and found much lower systematic absorption in small intestine than oral metronidazole.\textsuperscript{48} The pectin-metronidazole (PT-ME) prodrug was reported by Vaidya et al showed significantly reduced drug release in the upper GIT compared to pectin microspheres containing metronidazole exhibited nearly 100% entrapment and no release in the acidic region of stomach and successfully target to colon.\textsuperscript{49} Modasiya et al. have described the use of sodium alginate (Na-Alg) and hydroxypropyl methylcellulose (HPMC) as carriers for the successful delivery of curcumin by matrix, enteric-coated, and compression-coated tablets to the colon.\textsuperscript{50} Lack of versatility in formulating prodrug which depends upon the functional group available on the drug moiety for chemical linkage limits its usage and need a lot of evaluation before being used as carriers.\textsuperscript{51}

2. Newly developed approaches

2.1. pH sensitive polymer coated colon drug delivery system:
GIT have varied pH range responsible for efficient digestion of food or drug which increases or decreases during fasting, fed or diseased state. The inconsistency of pH ranges between 1 and 2 during fasting but increases after eating. The pH in small intestine is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine.19 Significantly declination of pH from the ileum to the colon to about 6.4 in the ceacum. Again decreases in the pH values as low as 5.7 have been measured in the ascending colon and 20 the pH in the transverse colon is 6.6 and 7.0 in the descending colon in healthy volunteers. Thus to compete with this environment throughout the GIT, use of pH sensitive polymers have been taken into consideration which provide suitable environment for drug to deliver to the colon. Drugs used in colonic diseases should reach to colon in high concentration, which gets hindered due to drug characteristics of dissolving in stomach owing to water solubility and acidic pH condition. Such moieties are coated with the biodegradable polymers have less or no solubility in upper part of GIT, when reaching to colonic site gets dissolve and release the entire drug. Another method than coating is embedding drug molecule in the matrices formed of pH sensitive polymer where drug released on reaching to colon from matrices. These processes have gained the advantage of enhance bioavailability and reduced dose frequency.41,52

2.2. Delayed (Time controlled) released system:
Sustained or delayed release dosage forms are one of the time-controlled release systems is very promising but as there is high variation in the gastric emptying time of dosage forms due to which exact arrival of dosage form into the colon cannot be predicted, in that way reducing bioavailability. These dosage forms can be appropriate for colon targeting by prolonging the lag time up to 5–6 h. Its feasibility has limited due to several demerits such as inconsistency in gastric emptying by type and amount of food intake, alteration in Git movements (peristalsis or contraction), Accelerated transit through different regions of the colon in diseased state. For achieving time-dependent systems, there should be the proper integration of pH sensitive as well as time-dependent approach to attain site-specific release of the drug into the colon.53,54,55

2.2.1. Pulsatile colon targeted drug delivery
a) Pulsincap system
The system is formulated in capsule form where the release of drug is controlled by using the plug in the capsule. The drug content is sealed within swellable hydrogels. Thus these hydrogels which get swelled up when come in contact with the dissolution fluid and after a lag time triggering the plug gets pushed off from the capsule and the drug will be released. Hydrogel plugs are mainly made up of polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate. The lag time is controlled by the length and point of intersection of the plug in the capsule body.56

b) Port system
This system in also a capsular body enclosed in a semipermeable membrane which comprises of an insoluble plug consisting the combination of osmotically active agent and drug formulation. As soon as the drug comes in contact with dissolution fluid allowing the fluid to enter via semi permeable membrane generates the pressure. The resulted pressure expels the plug out of the system and releases the drug at regular intervals with time gap between the successive intervals.57
3. Microbially triggered Colon Drug Delivery System (Enzyme based)

3.1. CODES technology

This CDDS is developed as combined approach of pH dependent and microbially triggered to minimize the difficulties associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers with polysaccharides are used, 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 system containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The outer coating is composed of the polymer Eudragit L which gets dissolved as soon as the tablet passes though the pyloric andduodenum and exposes the next coating. The another coating is composed of Eudragit E which allows the release of lactulose present in the inner core. This released lactulose lowers the pH of surrounding by metabolizing into short chain fatty acids that allows the layer of Eudragit E to dissolve leads to the exposure of drug to specific targeted area. The dissolving of Eudragit E results in the exposure of the drug. Some of the polysaccharides can be used along with drug in core tablet are mannitol, maltose etc. The colonic bacteria are responsible for the polysaccharides degradation releasing from core tablet that are released from the core tablet results in organic acids formation that lowers the pH of the contents surrounding the tablet.

3.2. Pressure Controlled Drug Delivery Systems

Peristalsis results higher pressure in the colon than in the small intestine. Takaya et al. have developed pressure controlled colon-delivery water insoluble ethylcellulose. In such systems drug release occurs subsequent disintegration of a water-insoluble polymer capsule resulting pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for disintegration of the formulation. Size of capsule and density of system plays an important role 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 bears the problem for oral delivery of drug specifically to colon. In pressure-controlled ethylcellulose single-unit capsules, liquid form of drug is present. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

3.2.1. Osmotically controlled colon targeted drug delivery system (ORDS-CT)

The OROS-CT (Alza corporation) is designed in a way which can be used either for targeting the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system contains osmotic units which may be single or as many as 5-6 push-pull units, each unit with dimension of 4-mm in diameter, encapsulated within a hard gelatin capsule. These units are bilayer with outer enteric impermeable membrane and inner semi permeable membrane. The drug resides in the internal or central part of the push pull with push payer. An orifice in semi permeable membrane present next to the drug layer expelled the drug during the course of time. After administration of capsule body enclosing the push pull units gets dissolved immediately. The enteric impermeable membrane prevents the water absorption when the unit pass through the GIT. The coating gets dissolved once it reaches the small intestine due to higher pH (>7) allows water enters the unit through the semi permeable membrane causing the push layer to swell. The resulted swelling of the push compartment forces the drug into the surrounding
environment through the orifice. These osmotic controlled drug delivery systems deliver the drug at a constant rate for up to 24 hr.4,17,56,63,64,65

4. Microparticulate systems
In the treatment of inflammatory bowel disease, sustained release devices like pellets, capsules or tablets have less efficiency due to diarrhoea, that enhances their elimination and reduction in total time availability for drug release. The symptomatic drawback is diarrhoea which results in speedy evacuation of drug carrier system with size larger than 200 µm causing decreased gastrointestinal transit time hence lowering the efficiency. Therefore, the optimum micron size for multiparticulate system is necessary for efficient working of dosage form. Lamprecht et al had reported the preparation of microparticles of tacrolimus (immunosuppressant drug) coated with Eudragit P-4135 F, a new pH sensitive polymer for colonic delivery.66 The various multiparticulate approaches for colon targeting include pellets, hydrogels, microparticles, microspheres, granules and nanoparticles.57,64 This system are chosen over single unit dosage forms enables the drug to reach the colon rapidly and reserved in colon for long period of time. Their smaller size add the benefits as by easily passing through GIT, uniform dispersion and more uniform drug absorption. Tahseen et al had reported Eudragit S-100 coated meropenem loaded pectin microspheres for the colon delivery where These microspheres maintain their integrity in upper part of GIT and reduce the side effects of the drug caused by its absorption from the upper part of GIT when the drug is given in conventional dosage forms such as tablets and capsules.67 Jain et al; had reported the formulation and evaluation of ethyl cellulose coated chitosan microspheres having antiamoebic drug (metronidazole) for colon delivery. The release of drug had witnessed was pH dependent.68

CONCLUSION
The present review focused on colon targeting drug delivery system which is on peak research status and has been widely and remarkably gaining its importance due to its efficiency and safety prospectus achieved tremendous growth and claim a good set of therapeutic applications.
Several approaches have been discussed above which give the interest for developing and take this topic to extreme good work. As the systemic delivery as well as local action of drug can be easily achieve without hindering the integrity of drug in the upper part of the GIT, making it advantageous over other conventional delivery system. This review has an intention to provide people in general vision of the field.
Future prospects
Colon targeting is one of the leading portion to be researched due to its specificity either in terms of maximum absorption of drug if reached in desired amount without getting lapsed to specific colonic site or for local action for the treatment of diseases like inflammatory bowel diseases. Recent studies sign post attention in colon as a site for poorly absorbed drug molecules to have improved bioavailability. The distal colonic part is measured to have less hostile environment and also less enzyme activity compared to stomach and small intestine. A formulations that can improve the oral absorption of peptide and protein drugs which is having very less bioavailability due to instability in the GI tract (due to pH or enzymatic degradation) is one of the extreme challenges for oral peptide delivery in the pharmaceutical
Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a stage for spatial delivery of drug moieties like peptides, proteins, oligonucleotides and vaccines. Nevertheless, release of drug is not the end point of oral delivery. The bioavailability of protein drugs delivered at the colon site requires to addressed. The enhancers for drug absorption are used into the drug delivery systems is likely to enhance therapeutic efficacy. Drug absorption by the intestinal system has engrossed on drug transporters that mediate drug influx and efflux and agents which can enhance drug absorption. The colonic part of GIT is designed by nature mainly to expel metabolized products rather than to absorb nutrients. Therefore, more researches are to be focused on the specificity of drug uptake at the colon site is necessary. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

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