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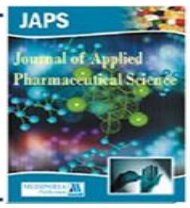

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Colon Specific Drug Delivery Systems: A Review on Various Pharmaceutical Approaches

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ABSTRACT

Colon specific drug delivery system has attracted considerable attention for the past few years in order to develop drug delivery systems that are able to release drugs specifically in the colon in a predictable and reproducible manner. The colon is a site where both local and systemic delivery of drugs can take place. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in the upper portion of the gastric intestinal tract (GIT) and then to be ensured abrupt or controlled release in the proximal colon. This review is aimed at understanding recent approaches for dosage forms which is targeting to colon through pH sensitive system, microbially triggered system i.e., prodrugs and polysaccharide based system, timed release system, osmotically controlled drug system, pressure dependent release system.

Keywords: Colon specific drug delivery, pH sensitive, time controlled dependent, microbially triggered, Pressure controlled and osmotically controlled system.

INTRODUCTION

Drug delivery to the colon 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. The colon specific drug delivery System (CDDS) 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, diarrhoea and colon cancer. Clinically relevant bioavailability may be achieved if the peptide can be protected from acid and enzymes in the stomach and upper intestine (Anil and Betty, 2010). The colon is having high water absorption capacity, 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 azo reduction and enzymatic cleavage i.e. glycosides. 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 (Chien, 1992).

Colon is rich in lymphoid tissue, eg., uptake of antigen into mast cells of colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. Region of colon is recognised as having a somewhat less hostile environment with less diversity and intensity of activity than stomach and small intestine (Chourasia et al., 2003) Target sites, colonic disease conditions, and drugs used for treatment are shown in Table 1 (Reddy et al., 1999).

Table1: Colon targeting diseases, drugs and sites.

Target sites	Disease conditions	Drug and active agents
Topical action	IBD, Irritable bowel disease Crohn's disease Chronic pancreatitis	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Olsalazine, Mesalazine.
Local action	Pancreatactomy cysti fibrosis Colorectal cancer	Digestive enzyme supplements 5-Flourouracil.
Systemic action	To prevent gastric irritation and first pass metabolism of orally ingested drugs like peptides and vaccines	NSAIDS , Steroid ,Insulin Typhoid.

Advantages of CDDS over conventional drug delivery

Chronic colitis, namely ulcerative colitis and Crohn's disease are currently treated with glucocorticoids and other anti-inflammatory agents (Philip et al., 2008). Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppressant, cushinoid symptoms, and bone resorption (Kulkani et al., 1999).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 (Mcleod et al., 1994).

FACTORS AFFECTED IN THE DESIGN OF COLON SPECIFIC DRUG DELIVERY SYSTEM

The anatomy of the colon is shown in **Figure 1.** The GIT 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 (Sarasija et al., 2000). 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. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon and the values were shown in Table 2. 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 (Kopeck et al., 1992).

Table 2: Measures of different parts of colon.

Large intestine	Length (cm)
Ascending colon	20-25
Descending colon	10-15
Transverse colon	40-45
Sigmoid colon	35-40
Rectum	12
Anal canal	3

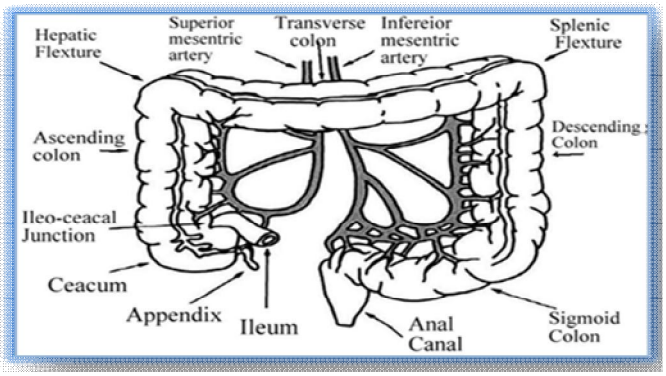

Fig 1: Anatomy of the colon.

Colon pH

The pH of the GIT is subject to both inter and intra subject variations. Diet, diseased state and food intake influences the pH of the gastrointestinal fluid. The changes in the pH along the gastrointestinal tract have been used as a means for targeted colon drug delivery. Radio telemetry shows the highest pH (7.5 ± 0.5) in the terminal ileum. On entry into the colon, the pH drops to 6.4 ± 0.6. The pH in the mid colon is 6.6 ± 0.8 and in the left colon 7.0 ± 0.7.There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by the colonic bacteria to produce large amounts of lactic acid resulting in pH drop to about 5.0 (Thomas et al.,1985; Avery et al., 1972).

Colonic microflora and enzymes

A large number of anaerobic and aerobic bacteria are present in the entire length of the human GIT. Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut microflora residing in high numbers in the colon. These enzymes are used to degrade coatings or matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug). Over 400 distinct bacterial species have been found 20 - 30% of which are of the genus bacteroids. The concentration of bacteria in the human colon is around 1000 CFU / mL. The most important anaerobic bacteria are bacteroides, bifidobacterium, eubacterium, peptococcus, peptostreptococcus, ruminococcus, and clostridium (Krishnaiah et al., 2001).

Transit of material in the colon

Compared to other regions of the gastrointestinal tract, movement of materials through the colon is slow. The total time for transit tends to be highly variable and influenced by a number of factors such as diet, in particular dietary fiber content, mobility, stress, disease and drugs. Colonic transit times ranged from 50 to 70 hours. Stool weights increased significantly with the presence of active disease presumably due to exudates form inflamed epithelium, increased mucus secretion and reduction in reabsorption of fluid and electrolytes (Rao et al., 1987).

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 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.

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, diarrhea, and colon cancer is ideal candidates for local colon delivery (Antonin et al., 1996; Fara et al., 1989; Mackay et al., 1993). The criteria for selection of drugs for CDDS are summarized in Table 3. 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 (Kothawade et al., 2011).

APPROACHES FOR CDDS

pH sensitive system

This approach is based on the pH-dependent release of the drug from the system. In this case the pH differential between the upper and terminal parts of GIT is exploited to effectively deliver drugs to the colon. One should not forget that the pH in the intestine and colon depends on many factors such as diet, food intake and intestinal motility and disease states.

This makes it more challenging for the specialists working in this field to design a delivery system that would be robust enough to withstand the variability in the gastric pH as it moves from the stomach to the small intestine. By combining knowledge of polymers and their solubility at different pH environments, delivery systems have been designed to deliver the drug at the target site (Evans et al., 1998). Commonly used copolymers of methacrylic acid and methyl methacrylate have been extensively investigated for colonic drug delivery systems. In vitro evaluation of Eudragit S and Eudragit FS was performed and it was found that the latter would be more appropriate for drug delivery to the ileocolonic region (Bussemer et al., 2001). Several factors, such as combinations of different polymers, pH of the media, coating level of the tablets and presence of plasticizers (Ashord et al., 1993).Inter and intra-subject variability, electrolyte concentration and transit time are some of the key variables impacting success through this route. In spite of these limitations, pH-based systems are commercially available for mesalazine (5 ASA) (Asacol® and Salofalk®) and budesonide (Budenofalk® and Entrocort®) for the treatment of ulcerative colitis and Crohn's disease, respectively.

Table 4: Enteric polymers used in the development of modified release formulations for CDDS

Enteric polymers	Optimum pH for dissolution
Polyvinyl acetate phthalate (PVAP)	5.0
Methacrylic acid copolymer, Type A	≥6.0
Eudragist FS30D	>7.0
Hydroxypropylmethylcellulose phthalate(HPMCP)	≥5.5
Methacrylie acid copolymer, Type C (Eudragit L100-55)	> 6.0
Methacrylic acid copolymer dispersion (Eudragit L30D-55)	> 5
Cellulose acetate trimelitate (CAT)	5.5
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	≥6.0
Shellac (MarCoat 125 & 125N)	7.0
Methacrylic acid copolymer, Type B	≥7.0

In general, the amount of coating required depends upon the solubility characteristics (solubility, dose/solubility ratio) of the drug, desired release profile and surface area of the formulation, and composition of the coating solution/dispersion. Coating approach is one of the simplest formulation technologies available for colon-specific delivery. It also offers significant advantage in terms of cost and ease of manufacture. From formulation standpoint, coated dosage forms may be either single-unit system or a multi-particulate system and each of these may be a single layer product or a multi-layer product.

Table 3: 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

In case of single layered products, the coating may be composed of a single enteric polymer that has a pH-dependent solubility or a mixture of two polymers one of which is pH-dependent while other is pH independent. On the other hand, in case of multilayer products, the coating is applied in successive layers which could be either based on two enteric polymers that have different pH-dependent solubility profiles, or two polymers one of which is enteric while other has a pH independent solubility but permeable to intestinal fluids. In either case, the coating can be applied to a wide variety of solid core formulations such as tablets, capsules, minitablets, pellets or granules. When coated pellets orgranules are filled into a gelatin capsule or compressed together with conventional excipients in the form of tablets, the formulation is regarded as multi-particulate dosage form. The tablets or capsules containing coated pellets or granules can be further coated with a suitable enteric polymer which may be same or different than that used for coating of pellets or granules. Modified-release formulations that are based on the combination of a pH-dependent and pH-independent polymer are described in a European patent assigned to Aktiebolaget Hässle. The approach involves coating of an active ingredient (e.g., mesalazine) with a mixture of an anionic acrylic polymer soluble just at pH 5.5 (e.g., Eudragit L) and a cationic acrylic polymer insoluble in water (e.g., Eudragit RS or RL). The quantities of anionic acrylic polymers can range from 10 to 85% while that of pH independent polymers may vary from 15 to 90%. The blending with one or more polymers having a pH independent solubility thus prevents the active ingredient from being released too rapidly, once the soluble polymer has reached the optimum pH of solubilisation.

Example: Mesalazine (also known as mesalamine, 5-aminosalicylic acid or 5-ASA) tablets coated with Eudragit L-100 are commercially available as Claversal, Salofalk, Mesasalâ and Rowasa. These tablets can effectively deliver mesalazine to the terminal ileum and proximal colon in patients with inflammatory bowel disease.

A scintigraphic assessment of Claversal tablets in a group of thirteen patients with Crohn's disease and ulcerative colitis indicated that more than 70% of administered tablets disintegrated with amean disintegration time of 3.2 h after gastric emptying, resulting in drug dispersion in the distal (lower) small intestine and proximal colon. It is important to recognize that drug release from Eudragit-L coated products may start in theproximal small intestine, which has a luminal pH of 6.6. Consequently, a relatively thick coating may be needed to delay the drug release until the formulation reaches the terminal ileum and proximal colon. An alternate approach to overcome above issues is to use a polymer which is insoluble below pH 7.0. Rhodes and Evans described a non-sustained release solid formulation in the form of a capsule or tablet containing a pharmacologically active agent, for example mesalazine, for the treatment of ulcerative colitis and Crohn's disease. The formulation is coated with a 60 to 150 µ thick layer of an anionic polymer, which is insoluble below pH 7. This anionic polymer is preferably a partly methyl esterified methacrylic acid (i.e., copolymer of methacrylic acid and methacrylic acid methyl ester) in which the ratio of free carboxylic groups to ester groups is approximately 1:2. For aqueous coating, it is commercially available as Eudragit S- 100, which comprises 27.6-30.7% methacrylic acid units per g dry substance.

Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles, nanoparticles, and beads. Because of their smaller particle size as compared to single unit dosage form these systems are capable of passing through the GIT easily (Parul and Avinash, 2011). A multiparticulate formulation, which also consists of a plurality of multidose minitablet units each of size less than 5 mm. Each minitablet unit is composed of a core containing the drug and coatedwith two successive coating layers. The inner coat is composed of a pH-dependent polymer, for example, Eudragit® which starts dissolving at pH 7.0. The second (outer) coating polymer is pH-independent and substantially insoluble but permeable to intestinal fluids (e.g., ethylcellulose). The presence of pH-independent layer significantly delays the release of the drug and acts as a rate controlling membrane. When only pH dependent polymer was used (i.e., in absence of pH independent layer), the formulation was able to delay the drug release for 3 h only. There was a very low release of the drug in buffered solutions up to pH 6.2 (first 3 h) followed by a rapid drug release when the pH increased to 7.2. On the other hand, formulation based on two successive layer coatings released no more than about 10% drug after 3 h and no more than about 75% drug after 6 hrs in simulated gastric fluids.

The drug release characteristics of the formulation, as described above, does not change when the order of successive coating layers are reversed. However, when the polymers constituting these successive layers were mixed, no delaying effect was observed and results were very similar to that of formulation that utilized only pH-dependent polymer (Calanchi et al.,1999).

Time controlled or Time dependent system

Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GIT. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms. Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time-based. In these systems, the site of drug release is decided by the transit time of a formulation in the GIT, which makes it challenging to develop a formulation in order to achieve a precise drug release in the colon. Ideally, formulations are designed such that the site of delivery (i.e. colon) is not affected by the individual differences in the gastric emptying time, pH of the stomach and small intestine or presence of anaerobic bacteria in the colon. On an average, an orally administered dosage form takes about 3 hrs to travel through the length of the small intestine to the beginning of the colon. Compared to gastric emptying rate, the small intestinal transit time is relatively consistent (Gazzaniga et al., 1994; Fukui et al., 2000; Vassallo et al., 1992; Vonderohe et al., 1993).

A system in the form of a tablet formulation (patent assigned to Hoffman-La Roche Inc.), which could release the drug consistently in the colon via a time-dependent explosion mechanism. The formulation is comprised of three parts: (i) a central core containing the drug and swelling excipients (ii) an inner semi-permeable polymer membrane containing a plasticizer which allows water influx but prevents the outward diffusion of drug and (iii) an outer enteric-coating which dissolves at or above pH 5.5. The outer enteric coat keeps the tablet intact until it reaches the small intestine. Upon arrival in the small intestine, the enteric coat dissolves allowing for GI fluid to diffuse through the semi-permeable membrane into the core. As a result, the core swells during the transit of the tablet through the small intestine. Finally, after a consistent period of 4-6 h transit in the small intestine, the swollen core burst the semi-permeable membrane releasing the drug in the colon (Shah et al., 2000).

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 GIT (Sinha et al.,2003; Gurpreet et al., 2010). 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, Bifidobacterium and Eubacterum* etc., whose major metabolic process occurring in colon are hydrolysis and reduction. The enzymes present in the colon are:

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

The vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc. For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches.

These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer (Gliko et al., 1998).

Targeted prodrug Design

Classical prodrugs design often represents a non-specific chemical approach to mask unwanted drug properties such as low bioavailability, less site specific, and chemical instability. On the other hand, targeted prodrug design represents a new strategy for directed and efficient drug delivery. Particularly, prodrugs targeting to a specific enzyme or a specific membrane transporter, or both, have potential drug delivery system especially for cancer chemotherapy. Design approach to target specific enzyme or carrier substrate specificity in order to overcome various unwanted drug properties which requires considerable knowledge related to a particular enzyme or carrier system including their molecular and functional characteristics, which are of
two type:

(i) Targeting specific enzymes

Glycoside derivatives are hydrophilic and are poorly absorbed from small intestine, but once they reach colon, they can be effectively liberated by bacterial glycosidases to release the free drug and facilitates the absorption by the colonic mucosa. Glycosidic prodrug, dexamethasone glucoside appeared to be better candidate, about 60% of the prodrug reach caecum as a free steroids, while parent drug were absorbed in small intestine.

(ii) Targeting specific membrane transporters

When free steroids were administered orally, they were almost absorbed in the small intestine and less than 1% of the oral dose reached the colon. The use of azo compounds for colon targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrugs. Sulphasalazine, which was used for the treatment of rheumatoid arthritis, was later known to have potential in the treatment of IBD. This compound has an azo bound between 5- amino salicylic acid and sulphapyridine.

(iii) Polysaccharide based systems

The polysaccharide which is polymer of monosaccharide retains their integrity, because they are resistant to digestive action of GI enzymes, matrices of polysachharide are assessed to remain intact in physiological environment of stomach and small intestine, as they reach colon they are acted upon bacterial polysaccharidases and results in degradation of the matrixes. Family of natural polysaccharide has appeal to area of drug delivery as it comprised of polymer with large number of derivitizable groups, with wide range of molecular weight, varying chemical composition and form most low toxicity and biodegradability, yet a high stability (Table 5). Pectin is a polysaccharide which contain α- 1,4 D-galactouronic acid and 1,2 D- Rhamnose with D-galactose & D-arabinose side chains. A novel colonic drug delivery is investigated. *In-vitro* experiments demonstrated that high methoxy pectin, when applied as compression coat, proved capable of coat tablet during condition stimulating gastrointestinal environment and was susceptible to enzymatic attack.

In-vivo gamma scintigraphic studies confirmed the

in-vitro findings the pectin coating tablets indicate that disintegrating in the colonic region and illustrated that degradation by microflora, thus necessities in in the development of such derivatives of pectin which is less water soluble, Calcium pectinate, the insoluble salt of pectin was used for colon targeted drug delivery of Indomethacin (Rubeinstein et al., 1993). Turkoglu and urugulu reported pectin hpmc compressed core tablets of 5-amino salicylic acid for colon delivery, drug dissolution/ system erosion/ degradation studies were carried out in pH 1.2 and 6.4 buffers using pectinolytic enzymes, system was designed that transit time from the GIT and arrival time for colon is 6 h. It was found that pectin alone was not sufficient to protects the core tablets and hpmc addition was required to control the stability of pectin. The optimum concentration of 20% hpmc were preferred for 6h that corresponds to 25 - 30% erosion and after the influence of the pectinase system degrade faster and release 5- amino salicylic acid to the colon.

Table 5: Characteristics of various biodegradable polymers for colon targeted drug delivery.

Polysaccharide	General properties	Bacterial species
Amylose	Unbranched constituents of starch used as excipients in tablets formulatio	Bacteriods, Bifidobacterium
Arabinogalactone	Natural pectin, hemicelluloses used as thickening agents	Bifidobacterium
Chitosan	Deacetylated chitin used as absorption enhancing Agents	Bacteroids
Chondroitin sulfate	Mucosopolysaccharides contains sulphate ester group at 4 or 6 position	Bacteroids
Cyclodextran	Cyclic structure of 6, 7 or 8 units, high stability against Amylase, used as drug solubilising agent and absorption enhancer.	Bacteroids
Dextran	Plasma expanders	Bacteroids
Guar gum	Galactomman used as thickening agent	Bacteroids Ruminococcus
Pectin	Partial methyl ether commonly used as thickening agents plant cell wall	Bacteriods, Bifidobacterium Eubacterium

Pressure controlled system

The digestive processes within the GIT involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis (Spraycar et al., 1995). These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of feces. To author's knowledge, there is only one invention related to the development of pressure-controlled system for colonic delivery. This particular delivery system is in the form of a capsule, which is resistant to the pressures of the upper GIT but is collapsed in the large intestine due to increased pressure. The capsule shells are fabricated from ethyl cellulose and the collapse time of the capsule in the large intestine can be controlled by adjusting the thickness of the capsule shell wall. The preferred thickness of the capsule wall is about 35- 60 µm.

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 unattainable (Theeuwes et al., 1990). 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 **(Fig. 2).** 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), water enters the unit, causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semi permeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 h in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon. Various *in-vitro/ in-vivo* evaluation techniques have been developed and proposed to test the performance and stability of CDDS. GI pressure is another mechanism that is utilised to initiate the release drug at distal part of GUT.

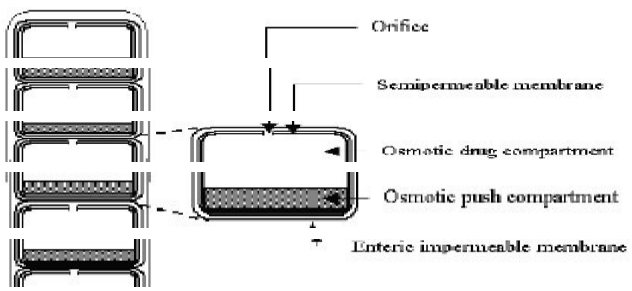

Fig 2: Cross-section of the oros-ct colon targeted drug delivery system.

CODESTM

CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release (Yang et al., 2002).

CONCLUSIONS

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Drug targeting to the diseased colon is advantageous in reducing the systemic side effects, lowering dose of a drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site. All the approaches of colon drug delivery provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs. The wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, makes the reliability, delivery efficiency of formulation and targeting to colon complicated.

REFERENCES

Anil KP., Betty Philip. Colon targeted drug delivery systems: a review on primary and novel approaches. Oman Medical Journal. 2010; 25.

Antonin KH., Rak R., Bieck PR., Preiss R., Schenker U., Hastewell J., Fox R., Mackay M. The absorption of human calcitonin from the transverse colon of man. Int J Pharm. 1996; 130(1):33-39.

Ashord M., Fell JT., Attwood D., Sharma H. Woodhead P. An evaluation of pectin as a carrier for drug targeting to the colon. J Control Rel 1993; 26:213-220.

Avery GS, Davies EF, Brogden RN. Lactulose: a review of its therapeutic and pharmacological properties with particular reference to ammonia metabolism and its made of action of portal systemic encephalopathy. Drugs. 1972; 4(1): 7-48.

Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carr Sys. 2001; 18: 433-458.

Calanchi M., Zema M., Brunetti G., Giorgetti. Timed pulsatile drug delivery systems. E: US5900252. 1999.

Chien YW. Oral drug delivery and delivery systems. In: Chien YW (Eds). Novel drug delivery systems. Marcel Dekker Inc. New York (1992) 139-196.

Chourasia MK., Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Sci. 2003; 6: 33-66.

Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 1988; 29: 1035-1041.

Fara JW. Novel Drug Delivery and its Therapeutic Application. In: Presscot LF, Nimmo WS (Ed.) Colonic drug absorption and metabolism. Wiley: Chichester. 1989; 103-120.

Fukui E., Miyamura N., Verma K., Kobayashi M. Preparation of enteric coated time released press coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting. Int J Pharm. 2000; 204.

Gazzaniga A., Iamartino P., Maffino G., Sangalli ME. Oral delayed release system for colonic specific drug delivery. Int J Pharm 1994; 108: 77.

Gliko-Kabir I., Yagen B., Penhasi A. Low swelling, crosslinked guar gum and its potential use as colon-specific drug carrier Pharm. Res 1998; 15: 1019.

Gurpreet K., Subheet J., Ashok KT. Investigations on microbially triggered system for colon delivery of budesonide. Asian J Pharm Sci 2010; 5: 96.

Kopeck J., Kopeckovap., Brondsted H., Rath R., Lkesuek. Polymers for colon-specific drug delivery, Journal of Controlled Release 1992; 19: 12-130.

Kothawade P. D, Gangurde HH, Surawase RK, Wagh M.A, Tamizharasi S. Conventional and novel approaches for colon specific drug delivery: a review.e-jst.2011; (2) 6: 33-56

Krishnaiah YSR., Satyanarayana S. In: Jain NK (Ed.) Advances in Controlled and Novel Drug Delivery New Delhi, India. 2001; 89- 119.

Kulkarni, S.K. Pharmacology of gastro-intestinal tract (GIT). In S. K. Kulkarni (Ed.) Book of Experimental Pharmacology. New Delhi: Vallabh Prakashan. 1999; 148- 150.

Mackay M, Tomlinson E(1993). Colonic delivery of therapeutic peptides and proteins, In: Biek PR, (Ed.) Colonic drug absorption and metabolism(pp. 159-176). New York: Marcel Dek ker.

McLeod AD., Friend DR., Thoma NT. Glucocorticoid-dextran conjugates as potential prodrugs for colon specific deliveryhydrolysis in rat gastrointestinal tract contents. J Pham Sci 1994; 83(9): 1284-1288.

Parul BP., Avinash SD. Multiparticulate approach: an emerging trend in colon specific drug delivery for Chronotherapy. Journal of Applied Pharmaceutical Science 01 (05); 2011: 59-63.

Philip AK., Dubey RK., Pathak K. Optimizing delivery of flurbiprofen to the colon using a targeted prodrug approach. J Pham Pharmacol 2008; 60: 607-613.

Rao SSC, Read NW, Bruce C, Brown C, Holdsworth CD. (1987) Studies of the mechanism of bowel disturbance in ulcerative colitis Gastroenterol: 93: 934-940.

Reddy MS., Sinha RV., Reddy DS. Colon targeted systems. Drugs Today 1999; 35(7): 537.

Rubinstein A., Radai R., Ezra M., Pathak S., Rokem JM. In vitro evaluation of calcium pectinate: A potential colon-specific drug delivery carrier. Pharm Res 1993; 10: 258

Sarasija S., Hota A. colon specific drug delivery system, Indian Journal of Pharmaceutical Sciences 2000; 62 (1): 1-8.

Shah NH., Railkar AM., Phuapradit, W.: US20006039975 (2000).

Sinha VR., Kumria R. Microbially triggered drug delivery to the colon. Eur J Pharm Sci 2003; 18: 3.

Spraycar M (Ed.) Stedman's Medical Dictionary, Maryland, Williams & Wilkins 1995; 1332-1333.

Theeuwes F., Guittard G., Wong P. Delivery of drugs to colon by oral dosage forms. US Patent 4904474, 1990.

Thomas P., Richards D., Richards A., Rojers L.,Evans BK, Drew MJ., Rhodes J. Absorption of delayed-release prednisolone in ul cerative colitis and Crohn's disease. Int J Pharm 1985; 37: 757.

Vassallo M, Camilleri M, Phillip SF, Brow ML, Chapman NJ, Thomforde GM. Transit through the proximal colon influences stool weight in the a irritable bowel syndrome. Gastroenterology 1992; 102: 102.

Vonderohe MR., Camolleri M., Kvols LK., Thomforde GM. Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. New Eng J Med 1993; 329: 107.

Yang L., James S., Joseph A. Colon specific drug delivery new approaches and *in vitro/ in vivo* evaluation. Int J Pharm 2002; 235.