Review Article

Novel Approaches to Colon Targeted Drug Delivery: An Overview

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ABSTRACT

The demand of the colon targeted drug delivery system has been increasing day by day because of its ability for acting as both locally and systemically. It provides local action for the colonic diseases like crohn's diseases, ulcerative colitis, irritable bowel syndrome etc and systemically for the delivery of proteins, peptides etc. This system also offers the advantage of reducing the first pass metabolism and to reduce the systemic toxicity of several drugs. The main of this method is to protect the drug from the upper GI tract and is important to reach the colon in intact form. There are several methods for achieving the above demand. 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: Colonic drug delivery, Drug targeting, Crohn's disease, inflammatory Bowel disease.

INTRODUCTION

The oral route of drug administration is considered as the most convenient method for the systemic effect because the patient acceptance for the oral administration of the drug is quite high and is relatively safe route of drug administration compared with parenteral route and potential damage at site of administration is minimal.[1] Colon delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. Colon). Therapeutic advantages of targeting drug to the diseased organ includes

- The ability to cut down the conventional dose
- Reduced the incidence of adverse side effects
- Delivery of drug in its intact form as close as possible to the target sites.[2]

Colon specific drug delivery systems are also gaining importance for the delivery of proteins and peptides due to several reasons as follow

- Rapid development of biotechnology and genetic engineering resulting into the availability of protein and peptide drugs at reasonable cost.
- Proteins and peptide drugs are destroyed and inactivated in acidic environment of the stomach or by pancreatic enzymes in small intestine.
- Parental route is expensive and inconvenient.
- Longer residence time, less peptidase activity and natural absorptive characteristics make the colon as promising site for the delivery of protein and peptide drug for systemic absorption.
- Less diversity, and intensity of digestive enzymes.[3]
- 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.

Advantages of Colon Targeting Drug Delivery System[4,5]

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon. Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Bye pass initial first pass metabolism.
- Extended daytime or nighttime activity.
- Improve patient compliance.
- Targeted drug delivery system.

- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route.

Limitations [6,7]

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

CRITERIA FOR SELECTION OF DRUG FOR CDDS[8]

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

FACTORS AFFECTED IN THE DESIGN OF COLON SPECIFIC DRUG DELIVERY SYSTEM

Anatomy of the colon[9]

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. 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.

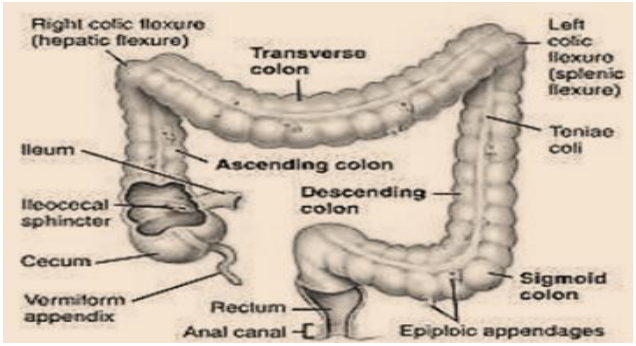

Figure 1: Anatomy of colon

Colon pH[10]

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

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.[11]

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.[12,13.24]

FORMULATION APPROACHES FOR COLON TARGETED DRUG DELIVERY

pH-dependent drug delivery systems

The colon exhibits a relatively greater pH than the upper Gastrointestinal tract, and this can be used as a targeting technique for colonic drug delivery systems. Accordingly, a colon-targeted drug delivery system is fabricated by using pH-dependent polymers like cellulose acetate phthalates (CAP), hydroxypropyl methyl-cellulose phthalate (HPMCP) 50 and 55, copolymers of methacrylic acid and methyl methacrylate (e.g., Eudragit® S 100, Eudragit® L, Eudragit® FS, and Eudragit® P4135 F). Eudragit® polymers are the mostly used synthetic copolymers for colonic drug delivery that cover mucoadhesiveness and pH-dependent drug release. The ideal polymer should be able to withstand in the low pH conditions of the stomach and the proximal part of the small intestine but it can be dissolved by the pH of the terminal ileum and the colon. As a result, drug delivery systems coated with pH-dependent polymers having a dissolution of pH 6.0–7.0 are expected to delays the drug dissolution and they can further prevent premature drug release in the upper GI tract before reaching colonic sites. However, this pH-dependent system has demonstrated significant variability in drug release and failure in vivo due to the vast inter- and intra-subject variability in the certain critical parameters including pH, fluids volumes, GI transit times, and motility. Furthermore, pH ranges of Gastrointestinal tract can be significantly altered by diet, disease state, water intake, and microbial metabolism. For example, the patients with ulcerative colitis exhibit more acidic colonic pH compared to the healthy humans, leading to incomplete drug release from enteric coated systems at the target site. Thus, the dynamic pH change by many internal and external factors may increases the efficiency of pH-dependent drug release systems, often leading to poorly site-selective drug release. Eudragit® S coating was not suitable for the colon-targeted drug release, may be due to disintegration failure at the target site or early drug release before the target site. To overcome the limitation of pH-dependent delivery systems, there have been attempts to use the combination of pH-dependent systems with other delivery systems including time-dependent systems and enzyme-triggered systems. For example, Eudragit® S were blended with high-amylose maize starch for the integration of pH-dependent system and colonic microbial degradation systems.[15,16]

Polymer-Based Nano-/Micro-Particles

Many studies have demonstrated that pH-dependent polymeric nanoparticles are effective as colonic drug delivery systems. In studies they used novel pH-sensitive hydrolyzed polyacrylamide-grafted-xanthan gum (PAAm-g-XG) for the colon-targeted delivery of curcumin nanoparticles. The amount of drug released from the PAAm-g-XG-modified nanoparticles was minimal in acidic conditions (pH 1.2 and 4.5), while faster and higher drug release from nanoparticles was observed at pH 7.2. Accordingly, the nanoparticles were effective in attenuating colonic inflammation and weight loss in IBD rat models. The blended mixture of two different pH-sensitive polymers can be used to control the drug release rate. Also studies developed the HBsAg-loaded nanoparticles by using the combination of Eudragit® L100 and Eudragit® S100 for effective colonic immunization, confirming the effective distribution of nanoparticles at the colon along with the improved immune response. To improve the site-specificity to the colon, fabricated budesonide-loaded pH-/time-dependent nanoparticles for the effective treatment of colitis. These nanoparticles were prepared with Eudragit® FS30D and Eudragit® RS100, using an oil-in-water emulsion solvent evaporation method. Eudragit® FS30D is a pH-dependent polymer that dissolves in an environment above pH 7.0, while Eudragit® RS100 is a time-dependent, controlled-release polymer having low permeability. Combining these two polymers effectively minimized premature drug release in the upper GI tract and achieved sustained-drug release throughout the colon.[17]

Lipid-Based Formulations

Liposomes are an efficient drug delivery system composed of double-layered phospholipids. Liposomes are biodegradable, biocompatible, and amenable to the incorporation of both hydrophilic and lipophilic drugs. The surface of liposomes can be coated with pH-dependent polymers to avoid the destabilization of liposomes in acidic conditions and also with ligands to improve the site-specificity. Studies developed colon-targeted liposomal formulations for sorafenib by coating the surface of anionic liposomes with glycol chitosan and pH-dependent Eudragit® S100. These liposomes showed high stability at acidic and neutral pHs with minimal drug leakage, which enhanced the systemic exposure of sorafenib in rats. Solid lipid nanoparticles are also a superior system in terms of drug protection, entrapment efficiency, and increasing the amount of drug released at specific sites. The lipid matrix of solid lipid nanoparticles degrades at a slow rate and allows for extended drug release.[18]

Tablets and Capsules

Colon targeted drug delivery can be achieved with film coated tablets or capsules even though there are few commercially available products. This system is applicable to macromolecules as well as low molecular synthetic drugs. Recently, developed the Eudragit L100-coated tablets for the colonic delivery of a novel anti-tumor necrosis factor domain antibody (V565). This tablet exhibited the sustained drug release at pH _ 6 but no drug release during 2-hr incubation in acidic conditions. In vivo

studies in monkeys also supported the sustained release of V565 in the intestine for the topical treatment of IBD. In addition, the drug release profiles can be manipulated by using a combination of copolymers with varying the ratios. This combination system may be superior to tablets coated with a single polymer for colon-targeted drug delivery. However, the tablets coated only with pH-sensitive enteric polymers still face the issues of premature drug release due to the variability of pH in GI tract. In addition, variability in the GI fluid composition, feeding status, and GI transit time affect the site-specific drug release from the pH-dependent system. Therefore, there have been continuous efforts to improve the targeting effectiveness via the multi-unit formulations based on the integration of the different mechanism-based systems with pH-dependent coating.[19]

Enzyme-Sensitive Drug Delivery Systems

Polysaccharide-Based Systems[20]

Microbiota-activated delivery systems have shown promise in colon-targeted drug delivery due to the abrupt increase of microbiota and the associated enzymatic activities in the lower GI tract. These systems are dependent on the specific enzyme activity of the colonic bacteria and the polymers degradable by colonic microorganisms. Particularly, polysaccharides such as pectin, guar gum, inulin, and chitosan have been used in colon-targeted drug delivery systems, because they can retain their integrity in the upper GI tract but are metabolized by colonic microflora to release the entrapped drug. New polysaccharides including arabinoxylans and agave fructans are also being explored for colonic drug delivery systems. Furthermore, structural modifications or derivatives of polysaccharides can improve drug release behavior, stability, and site specificity. Mucoadhesiveness of polysaccharides can be advantageous for drug uptake via the prolonged contact between the mucosal surface and drug delivery carriers. Polysaccharide-based delivery systems also have some additional advantages including availability at large scale, relatively low cost, low toxicity and immunogenicity, high biocompatibility, and biodegradability. Consequently, the polysaccharide-based, microbiota-triggered system is promising strategy for colon-specific drug delivery. However, polysaccharides-based delivery systems also have some potential drawbacks, which include broad range of molecular weights and variable chemistry of polysaccharides. In addition, low solubility in most organic solvents limits the chemical modification of polysaccharides, while hydrophilicity and excessive aqueous solubility of polysaccharides may cause the early and undesirable drug release in the upper GI tract. Accordingly, cross-linking agents are often used to overcome this issue. In addition, the lack of film forming ability, along with swelling and solubility characteristics of polysaccharides limits their application for colonic drug delivery.

Phloral® Technology[21]

The studies reported a novel colonic coating technology which integrated pH-dependent and bacterially-triggered systems into a single layer matrix film. Tablets were film-coated by using a mixture of Eudragit S and biodegradable polysaccharide. Gamma scintigraphy study in human volunteers confirmed the consistent disintegration of these tablets in the colon regardless of feeding status, suggesting that this dual-mechanism coating may overcome the limitation of single trigger systems and improve the colonic drug targeting. Subsequently, Phloral® coating technology demonstrated the precise and fail-safe drug release in the colon in both healthy and diseased states. This system consists of an enzyme-sensitive component (natural polysaccharide) and a pH-dependent polymer, where these pH and enzymatic triggers work in a complementary manner to facilitate site-specific release. Even if the dissolution threshold of the pH-dependent polymer is not reached, the enzyme-sensitive component is independently digested by enzymes secreted by colonic microflora. This additional fail-safe mechanism overcomes the limitations of conventional pH-dependent systems. This innovative technology has been validated in clinical studies for consistent drug release with reduced-intra subject variability in patients and healthy subjects. It is also applicable for the oral delivery of macromolecules such as peptides, proteins, and vaccines. Recently, scientists investigated the applicability of this technology in the colonic delivery of probiotics. The commercial products as well as in-house freeze-dried Lactobacillus acidophilus strain were encapsulated into capsules using dual-trigger coating technology to target the delivery into lower small intestines or colon. The viabilities of approximately 90% were retained after these capsules were exposed to gastric environment for 2 h while the unencapsulated probiotics showed poor tolerance to the gastric environment.

Ligand/Receptor-Mediated Drug Delivery System

For a more effective local treatment of colonic disease with reduced toxic side effects, ligand/receptor-mediated systems have been explored that increase target specificity via the interaction between targeting ligands on the carrier surface and specific receptors expressed at disease sites. Ligand/receptor-mediated system can be designed using various ligands (e.g., antibodies, peptides, folic acid, and hyaluronic acids) selected based on the functional expression profiles of specific receptors/proteins at the target cells/organs. It can be also combined with pH-dependent systems to maximize its GI stability and site specificity, if needed.[22]

Antibodies

Th prepared anti-transferrin receptor antibody-conjugated liposomes, demonstrating better cellular internalization of the conjugated liposomes than unconjugated liposomes. Furthermore, anti-transferrin receptor antibody-conjugated liposomes exhibited preferential distribution to the inflamed mucosa rather than normal mucosa,

resulting in greater accumulation at the site of inflammation (more than 4-fold higher) when compared to that of normal mucosa. Also developed nanoparticles fabricated with single-chain CD98 antibodies on their surface (scCD98-functionalized) for IBD therapy. CD98 is a heterodimeric neutral amino acid transporter, which is overexpressed in intestinal macrophages and colonic epithelial cells in mice with colitis. Sc CD98-functionalized nanoparticles exhibited a high affinity for CD98-overexpressed cells. In mice with colitis, scCD98-functionalized nanoparticles containing CD98 siRNA (siCD98) reduced the expression levels of CD98 and the severity of colitis in mice.[23]

Folic Acid

Folic acid, a water-soluble vitamin, is a tumor-selective targeting ligand because the folate receptor is overexpressed in many types of cancers. Many studies have demonstrated that nanoparticles decorated with folic acid can facilitate tumor-selective drug uptake. Folic acid-conjugated liposomes improved the anti-cancer activity of daunorubicin by facilitating folate receptor-mediated drug uptake. Also, the different techniques fabricated folic acid (FA)-conjugated liposomes containing 5-fluorouracil (5-FU). 5-FU loaded FA-liposomes exhibited higher cytotoxicity and significantly reduced tumor volume when compared to free drug. These results indicate that folic acid-targeted liposomes may be an effective drug carrier that can increase selective drug delivery to cancer cells. A folate-modified self-microemulsifying drug delivery system (FSMEDDS) containing curcumin can also be a means of improving drug solubility as well as its delivery to the colon. Their results confirmed that an FSMEDDS could reach the colon efficiently and release its drug payload rapidly. Furthermore, the FSMEDDS formulation could actively target tumor cells overexpressing folate receptors, indicating that an FSMEDDS may be a promising carrier for the colonic delivery of curcumin.[23]

Hyaluronic Acid

Hyaluronic acid (HA) is a natural polysaccharide consisting of disaccharide units of d-glucuronic acid and N-acetyl-d-glucosamine. Since HA has a high affinity for the CD44 receptor, which is overexpressed in various cancers, HA-conjugated drug delivery systems have been examined for target-selective drug delivery. For example, previous studies have examined the effectiveness of HA-modified mesoporous silica nanoparticles targeting the CD44-overexpressing cancer cells. Developed self-assembled HA nanoparticles as colonic carriers of budesonide for targeting inflamed intestinal mucosa. Budesonide loaded HA nanoparticles exhibited higher uptake in inflamed cells over-expressing CD44 receptors, leading to a decrease in IL-8 and TNF-_ secretion in an inflamed cell model. Accordingly, HA-conjugated nanoparticles appear to be a promising targeted drug delivery system for IBD treatment. HA nanoparticle-based combination chemotherapy to create synergistic, targeted drug delivery system for colon cancer therapy. They prepared HA-functionalized camptothecin (CPT)/curcumin (CUR)-loaded polymeric NPs (HA-CPT/CUR-NPs) approximately 289 nm in size with a negative zeta potential. HA-CPT/CUR-NPs exhibited significant cancer-targeting capability against Colon-26 cells. They also investigated a simultaneous delivery system of curcumin (CUR) and CD98 siRNA (siCD98), using hyaluronic acid (HA)-functionalized polymeric nanoparticles. Compared to the single drug-based monotherapy, co-delivery of siCD98 and CUR by HA-functionalized nanoparticles exhibited an enhanced therapeutic effect against ulcerative colitis by protecting the mucosal layer and alleviating inflammation. Therefore, HA-functionalized polymeric nanoparticles may be an efficient colonic delivery carrier for combination drug therapy.[23]

Peptides

Peptide gains a great attention as a potential ligand for targeted drug delivery. Peptides possess many advantages including biocompatibility, cost-effectiveness, chemical diversity, and stimuli responsiveness. In addition, compared to small molecule ligands, peptide ligands exhibit much higher binding affinity and specificity due to the large binding interfaces with receptors. Peptide ligands are also advantageous due to their accessibility of high-throughput screening and ease of synthesis by using automated solid-phase peptide synthesis devices. Furthermore, the metabolic instability by proteases can be overcome via the modification of the peptide sequences, promoting the application of peptide ligands in targeted drug delivery systems. Particularly, peptide-conjugated drug delivery systems are explored as a viable approach for tumor-targeted drug delivery.[24]

Magnetically-Driven Drug Delivery System

Magnetic microcarriers including magnetic microspheres, magnetic nanoparticles, magnetic liposomes, and magnetic emulsions are emerging novel formulations for controlled and targeted drug delivery. To improve the targeted treatment of colorectal cancer by mAb198.3 (a FAT1-specific monoclonal antibody) scientists developed two different novel drug delivery systems having magnetic properties to improve the targeted treatment of colorectal cancer by mAb198.3 (a FAT1-specific monoclonal antibody), where mAb198.3 was directly bound to super-paramagnetic nanoparticles or embedded into human erythrocyte-based magnetized carriers. They observed that both systems were very effective at targeting colon cancer cells and inhibiting cancer growth at significantly lower antibody doses. This study demonstrated the potential of magnetically-driven drug delivery systems at improving the bioavailability and target specificity of anti-FAT mAb198.3, opening a new avenue for colon-targeted drug delivery. Another previous study improved the efficacy of hydrocortisone using a magnetic belt on rats. This nanodevice consisted of magnetic mesoporous silica microparticles loaded with hydrocortisone. The outer surface of the drug-loaded nanoparticles was functionalized with a bulky azo derivative with urea

moieties. The nanodevices remained capped at neutral pHs, but a noticeable payload release occurred in the presence of sodium dithionite because it reduced the azo bonds in the capping joint. They also observed the improved efficacy in rats wearing magnetic belts, particularly being more effective when a magnetic field was externally applied to lengthen the retention time in the areas of interest. This study demonstrated that the use of a magnetic belt increased the drug efficacy in the treatment of IBD due to enhanced retention time of the drugs in the colon.[24,25]

Pulsatile Colon Targeted Drug Delivery:[26]

1) Pulsincap System: These (single-unit) systems are mostly developed in a capsule form. The drug is released as a "Pulse" from the insoluble capsule body by swelling or erosion of plug (control lag time). A swellable hydrogel plug was used to seal the drug contents into the capsule body, and when in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The length of the plug and its point of insertion into the capsule controls the lag time.

2) Port System: This system based on the principle of delayed drug release. This system consists of:

- Gelatin capsule coated with a semi-permeable membrane (*g*., cellulose acetate) housing,
- An insoluble plug (*g*., lipidic),
- An osmotically active agent along with the drug formulation.

Pressure Controlled Drug-Delivery Systems

Contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents required for the digestive process. The pressure generated by muscular contraction of the gut wall is responsible for the grinding and propulsion of the intestinal contents, and changes in the intensity and duration throughout the GI tract, while the colon is considered to have higher luminal pressure due to the process that occurs during stool formation. As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules prepared using ethylcellulose, which is insoluble in water.[27] In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation.[28,29] 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 ethylcellulose single unit capsules the drug is in a liquid.[30] Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

Novel Colon Targeted Delivery System (CODESTM)

CODESTM is a unique CDDS technology and overcomes problems associated with pH or time-dependent systems. It is a combined approach of pH-dependent and microbially triggered CDDS. A unique mechanism involving lactulose acts as a trigger for site-specific drug release in the colon CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems.[31,32] 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 effect the dissolution of the acid soluble coating and subsequent drug release.

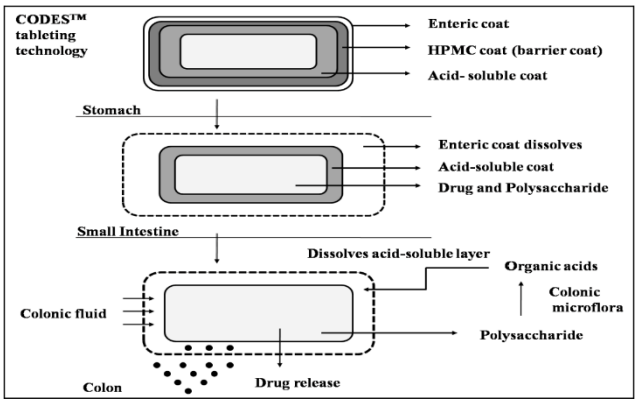

Figure 2: Mechanism of CODESTM

Osmotic Controlled Drug Delivery (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. 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.[33] Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. 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 semipermeable 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 hours 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.[34,35,36] Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

CONCLUSION

Improved drug delivery systems are required for drugs currently in use to treat localized diseases of the colon. The advantages of targeting drugs specifically to the diseased colon are reduced incidence of systemic side effects, lower dose of drug, supply of the drug to the biophase only when it is required and maintenance of the drug in its intact form as close as possible to the target site. 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

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