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Drug Delivery System as Colon Targeting: An overview

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ABSTRACT

The oral route is measured to be the most preferred route for administration of drugs for systemic effect, but the oral route is not appropriate to the administration of drug for lower gastrointestinal (GI) diseases, this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the convenience of drugs at the lower GI tract. To overcome this complexity, colon-specific drug delivery systems have been largely analyzed throughout the last two decades. Colonic drug delivery has gained increased significance not just for the delivery of the drugs for the cure of local diseases associated with the colon like Crohn's disease, ulcerative colitis, *etc*. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs, and anti-diabetic agents. This review article discusses, in concise, the introduction of the colon, factor affecting the colonic transition, colonic diseases and the novel and rising technologies for colon targeting. Major approaches for Colon Colon targeted Drug Delivery System, which include prodrugs, pH and time dependent systems, Bacterial enzyme dependent colonic Drug Delivery System and pH and bacterial enzyme dependent colonic Drug Delivery System. The novel approach of CTDDS, which includes pressure controlled colonic delivery capsules, osmotic controlled drug delivery are precise technique..

Keywords: Novel approaches, evaluation of colon targeted drug delivery systems (CTDDS)

INTRODUCTION

Targeted drug delivery into the colon is very highly advantageous for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon specific drug delivery system 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 is supposed to be a suitable absorption site for peptides and protein drugs for the following reasons;

- Less assortment, and intensity of digestive enzymes,
- Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine.

So Colon Drug Delivery System protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to larger systemic bioavailability. Hence finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers. Oral route is the most convenient and preferred route but other routes for Colon Drug Delivery System may be used.Rectal route of administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and conformity may be less than optimal. Drug preparation for intra-rectal administration is supplied as solutions, foam,

and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity. Because of the high water absorption capacity of the colon, 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 azoreduction 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. (3,6,8,9,16,17, 20,21)

COLON TARGETING DRUG DELIVERY SYSTEM

Colon targeting Drug Delivery system may be follow the perception of sustained or controlled drug delivery system, for colon targeting drug delivery system oral route of administration has received most attention. This is because of the flexibility in dosage form designed for oral than parenteral route because.

- Patient acceptance for the oral administration of the drug is quite high.
- It is relatively safe route of drug administration compared with parenteral route and potential damage at site of administration is minimal.

Mainly of the conventional drug delivery systems for treating the colonic disorder such as Inflammatory bowel diseases i.e. Ulcerative colitis, Cohn's diseases, Colon cancer and Amoebiasis are failing as drug do not reach the site of action in appropriate concentration. For effective and safe therapy of these colonic disorders, colon specific drug delivery is necessary. Today, colon specific drug delivery is challenging task to pharmaceutical technologists. Therapeutic advantages of targeting drug to the diseased organ include. Therapeutic advantages of targeting drug to the diseased organ includes. (7,8)

- The capability to cut down the conventional dose
- Reduced the occurrence of adverse side effects
- Delivery of drug in its integral form as close as possible to the target sites.

Colon particular drug delivery systems are also gaining importance for the delivery of protein 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 ruined 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.
- Fewer diversity, and intensity of digestive enzymes.
- Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus Colon Drug Delivery System 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.

ADVANTMENT OF COLON TARGETING DRUG DELIVERY SYSTEM OVER CONVENTIONAL DRUG DELIVERY

Chronic colitis, namely ulcerative colitis, and Crohn's disease are currently treated with glucocorticoids, and other anti-inflammatory agents. Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppression, cushinoid symptoms, and bone resorption. 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.(8)

CRITERIA FOR SELECTION OF DRUG FOR COLON DRUG DELIVERY SYSTEM(19)

COLON TARGETING DRUG DELIVERY SYSTEM is 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 pas metabolism
- Drugs poorly absorbed from upper GIT
- Drugs for targeting

FACTORS TO BE AFFECTED IN THE DESIGN OF COLON - TARGETED DRUG DELIVERY SYSTEM (8,19,14)

ANATOMY AND PHYSIOLOGY OF COLON

The GI tract is alienated 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. 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**.**

pH inside the colon

The pH of the Gastro-Intestinal tract 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 GI 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 existence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by the colonic bacteria to produce big amounts of lactic acid results in pH drop to about 5.0.

Colonic Micro floral Enzymes

A huge number of anaerobic and aerobic bacteria are present in the entire length of the human GI tract. Intestinal enzymes are used to trigger drug release in various parts of the GI tract. typically, these enzymes are derived from gut micro flora residing in high numbers in the colon. These enzymes are used to degrade coatings or matrices as well as to split 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 significant anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, and Peptostreptococcus, Ruminococcus, Clostridium.

Transit of Material inside the Colon

The presence of food material generally increases gastric residence and in some cases with regular feeding, dosage forms have been shown to reside in the stomach for periods in excess of 12 hours. Small intestinal transit is startlingly constant at 3-4hours and appears to be sovereign of the type of dosage form and whether the subject is in the fasted or fed state. 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, improved mucus secretion, and reduction in reabsorption of fluid and electrolytes.

Drug absorption inside 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 involve the transfer of drug through the tight junction between cells and is the route most hydrophilic drug takes.The poor paracellular absorption of many drugs in the colon is due to the fact that epithelial cell junctions are very tight. 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. Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum. The oral absorption of the majority of peptide and protein drugs is limited because of following reasons:

- Degradation in the acidic environment of the stomach.
- Enzymatic degradation in the small and large intestine.
- Rapid small intestine transit.
- Low mucosal permeability.
- Extensive first pass metabolism by the absorbing membrane and the liver.

APPROACHES OF COLONIC DRUG DELIVERY SYSTEM(7)

In general, seven primary approaches have been proposed for targeted colon delivery, namely, Transit time dependent colonic drug delivery system pH Dependent colonic drug delivery system
pH- and time-dependent colonic drug delivery system Bacterial enzyme dependent colonic drug delivery system Prodrug based system.

Transportation time dependent colonic Drug delivery system

Transit time dependent colonic drug delivery system such as sustained or delayed release dosage forms are one of important drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h. However, the disadvantages of this system area. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

pH Dependent colonic drug delivery system

The pH-dependent colon targeting drug delivery system exploit the generallyaccepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, how- ever, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ile-ocecal junction. These processes distribute the drug throughout the large intestine and improve the potential of colon targeted delivery systems. While this release pattern can be studied in-vitro, there is no real substitute for confirming reliable performance in vivo in man.The technique of gamma scintigraphy has become the most popular method to investigate the gastrointestinal performance of pharmaceutical dosage forms. The threshold pH commonly employed pH-sensitive polymers.

pH- and time-reliant colonic DDS(1,2,3,4,5,6,7)

The transit time throughout the small intestine is independent of the formulation. But, the time taken by the formulation to depart the stomach varies greatly. Hence, the time of arrival of a formulation in the colon cannot be accurately predicted. However, the effects of variation in gastric residence time can be reduced by using systems that prevent drug release until 3-4 hr after leaving the stomach. A multiple coated oral dosage form consisting of core coated with three polymeric layers has developed. a novel oral time based drug release system for colonspecific delivery.The system designed to exploit the relatively constant small intestinal transit time of dosage forms consists of drug-containing cores coated with three polymeric layers. The outer layer dissolves at pH > 5, then the intermediate swellable layer, made of an enteric material. The system provides the expected delayed release pattern, as also indicated by the preliminary in vivo studies on rats. Several other drug delivery systems have developed that rely upon the relatively constant transit time of small intestine. A new delivery system was developed for delivering drugs to the colon by selecting polymethacrylates with appropriate pH dissolution characteristics for the distal end of the small intestine. Pellets were prepared by powder layering of 5-ASA on nonpareils (0.5-0.6 mm) in a conventional coating pan. Drug- layered pellets were coated with an inner layer of a combination of two pH-independent polymers Eudragit RL and RS (2:8), and an outer layer of a pH-dependent polymer, Eudragit® FS. In another method, an organic acid (succinic acid) was filled into the body of a hard gelatin capsule as a pH- adjusting agent together with the drug substance. The joint of the capsule was sealed using an ethanolic solution of ethyl cellulose. The capsule was first coated with an acid soluble polymer (Eudragit E), then with a hydrophilic polymer HPMC and finally enterically coated with Eudragit L. After ingestion of the capsule, the outermost enteric layer of the coating prevents drug release in the stomach. Enteric layer and hydrophilic layers dissolve quickly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid, the acid soluble layer dissolves and the enclosed drug is quickly released. Therefore, the onset time of drug releases in the intestine can be controlled by the thickness of acid soluble layer(7,8).Drug targeting to colon would be prove useful where intentional delayed drug absorption is desired from therapeutic point of view in treatment of circadian diseases that have peak symptoms in the early morning such as nocturnal asthma, angina pectoris and rheumatoid arthritis.Colon specific drug delivery systems are gaining the importance for systemic as well as local effect. Colon specific drug delivery system is popular for treatment of inflammatory bowel diseases (IBD), delivery of protein and peptide drugs, for circadian diseases and also for improving the systemic absorption of the some drugs, additionally following chart help in selection of drug candidate for colon specific drug delivery .(7,8,19)

Bacterial enzyme dependent colonic DDS (7,18,12,22)

The colonial microflora is in the range of 1011-1012 Cfu/ml consisting mainly of anaerobic bacteria, e.g. Bacteroides Bifid bacterium, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. This microflora fulfill its energy desires by fermenting various types of substrates that have been left undigested in the small intestine, like di- and trisaccharides, polysaccharides etc. For this fermentation, the micro flora 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.The majority of bacteria are present in the colon they are distributed throughout the GI tract. Endogenous and exogenous substrates, such as carbohydrates and proteins, escape digestion in the upper GI tract but are metabolized by the enzymes secreted by colonic bacteria.Sulphasalazine, a Prodrug consisting of the active ingredient mesalazine, was the first bacteria sensitive delivery system designed to deliver the drug to the colon. Use of polysaccharides offers an alternative substrate for the bacterial enzymes present in the colon. Most of the polymers are used in pharmaceutical compositions and are considered generally regarded as safe (GRAS) recipients

Prodrug based system

A Prodrug is a pharmacologically inactive derived of a parent molecule that requires some form of transformation in vivo to release the active drug at the target site. This approach involves covalent linkage between the drug and its

carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. The type of linkage that is formed between the drug and carrier would decide the triggering mechanism for the release of the drug in the colon. This biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon. The enzymes that are mainly targeted for colon drug delivery include azoreducatase-galactosidase, β- xylosidase, nitroreductase, glycosidase deaminase, etc.Generally, a prodrug is successful as a colon drug carrier if it is hydrophilic and bulky, to minimize absorption from the upper GI tract and, once in the colon, it is converted into a more lipophilic drug molecule that is then available for absorption.. They break down upon action of glycosidase, releasing the drug part form the sugar. Glycosidase activity of the GI tract is derived from anaerobic microflora in the large bowel or exfoliated cells of the small intestine. 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.

Azo Prodrugs

The azo linkage exhibits a wide range of thermal, chemical, photochemical and pharmaceutical properties. The azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic components and extracellular reduction.The use of these 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 inflammatory bowel disease (IBD). This compound has an azo bond between 5-ASA and sulphapyridine.

Polymeric or Saccharide Prodrug

The use of naturally occurring polysaccharides is attract a lot of attention for drug targeting the colon since these polymers of mono saccharides are found in abundance, have wide availability are inexpensive and are available in a verity of a structures with varied properties. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccrides can be broken down by the colonic microflora to simple saccharides. Therefore, they fall into the category of "generally regarded as safe" (GRAS). Chitosan is a high molecular weight cationic polysacacharide, poly (Nglucosamine), derived from chitin in crab and shrimp shells by deacetylation. It is degraded by the rich colonic microflora. Chitosan has been evaluated for colon specific drug delivery mainly in the form of a capsule forming material. Pectin is another non-starch linear polysaccharides with mainly a-(1-4)- linked Dgalacturonic acid residues interrupted by 1, 2- linked Lrhamnose.

Polymeric Prodrugs

Azo-linked polymeric prodrugs of 5-ASA were prepared and evaluated in simulated human intestinal microbial eco-system. Polyamides containing azo groups in the backbone were prepared and tested in vitro in a reductive buffer or in the bioreactor medium. It was demonstrated that for the hydrophobic polymer, reduction stopsAs films at the hydrazine stage whereas for a hydrophilic analogue reduction with formation of amine occurred. The amount of the drug released depends on the nature of the polymer and can approach that of low molecular weight Prodrugs.

Amino acid Prodrug

Hydrophilic nature of polar groups like -NH2 and -COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to SA. The prodrug was absorbed into the systemic circulation from the upper GIT and hence it was proved unsuitable for delivery of drugs to the colon. By increasing the hydrophilicity and chain length of the carrier amino acid and decreasing the membrane permeability of conjugate Nakamura et al. prepared salicylic glutamic acid conjugates. This conjugate showed splendid results with minimal absorption and degradation in the upper GIT and proved suitable for colon targeted delivery of SA.Glycine and glutamic acid conjugates of salicylic acid. (a) Salicyluric acid. (b) Salicyl Glutamic acid conjugate.

pH and bacterial enzyme dependent colonic DDS (CODES SYSTEM)

CODES system is a unique COLON TARGETING DRUG DELIVERY SYSTEM(11,12,13,14,15)technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODES system is a combined approach of pH dependent and microbially triggered Colon Drug Delivery System. 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 enzymetically 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.

Colonic pressure controlled drug delivery system (PCDC SYSTEM) (15,147,23)

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Developed pressure controlled colon- delivery capsules prepared using ethylcellulose, which is insoluble in water. 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. 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. Lag times of three to five hours in relation to drug absorption were noted when pressure controlled capsules were administered to humans.

Osmotic pressure controlledcolonic DDS(18,19,20,21)

Osmet Pump (ALZET)

ALZET® Osmotic Pumps are miniature, infusion pumps for the continuous dosing of unrestrained laboratory animals as small as mice and young rats.These minipumps provide researchers with a convenient, reliable, and cost-effective method for controlled delivery of agents. ALZET miniosmotic pumps require no external connections or researcher intervention during the entire delivery period. Their unique design helps researchers save critical time by eliminating the need for frequent animal handling and repetitive injection schedules.These dependable drug delivery systems ensure that constant levels of compounds be maintained at therapeutic levels, thus avoiding potentially toxic or misleading side effects. An assortment of sizes, flow rates and durations is available to meet a variety of research needs. A single ALZET pump provides up to 6 weeks of continuous infusion.

OROS CT

The OROS-CT 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 single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule . Each bilayer push pull unit contains an osmotic push layer and a drug layer, both sur- rounded by a semi-permeable 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 aque- ous environment of the stomach and hence no drug is delivered. As the unit enter the small intestine, the coating dissolve 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 con-trolled by the rate of water transport through the semipermeable membrane.For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour 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 an internal as short as 4 hour.

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